Editors

The abstracts were marked by the Abstract marking Panel selected by the programme Organising Committee

ECE 2013 Programme Organising Committee

Justo Castaño Chair

Members

Paolo Beck-Peccoz
Philippe Bouchard
Thierry Brue
Mark Cooper
Evanthia Diamanti-Kandarakis
Carlos Dieguez

Sevim Gullu
Ilpo Huhtaniemi
Laszlo Hunyady
Dragan D Micic
Kjell Öberg
Marija Pfeifer

Martin Reincke
Paula Soares
Anna Spada
A J van der Lely
Antonio Vidal-Puig
Maria C Zatelli

Abstract Marking Panel

B Abrahamsen Denmark
S Ali UK
B Altun Turkey
A Aranda Spain
G Ayvat Turkey
P Beck-Peccoz Italy
N Biermaas NL
J Boren Sweden
H Boztepe Turkey
T Brue France
C Buchanen UK
M J Bugalha Portugal
J M Cameselle Spain
F Carrolho Portugal
D Carvalho Portugal
J Christiansen Denmark
P Clayton UK
M Cooper Australia
S R Cuenca Spain
O Deynelli Turkey
E Diamanti-Kandarakis Greece
C Dieguez Spain
S Djamjanovic Serbia
R Dullaart NL
T Erbas Turkey
M Erdogan Turkey
A Faggiano Italy

J-M Fernandez-Real Spain
C Follin Sweden
C Forsblom Finland
F Gatto Italy
N Gattoes UK
D Gogas Turkey
L Gomes Portugal
F Gracia-Navarro Spain
A Garlek Turkey
A Garsoy Turkey
N Hamdy NL
T Hansen Denmark
A Hermus NL
S Herzig Germany
M Hewisdiction USA
L Hofbauer Germany
E Hommel Denmark
J Huhtaniemi UK
J Jacomme de Castro Portugal
J O Jørgensen Denmark
A Juul Denmark
N Karavitaki UK
M Keil USA
F Kestelum Turkey
M Kebbonits UK
R Laque Spain
P Lear UK

C Lemos Portugal
S Llahama UK
J Loma Portugal
J-M Lopes Portugal
M Lopez Spain
G Lavery UK
M Malagon Spain
M Melo Portugal
D Micic Serbia
J Mittag Sweden
M Monteiro Portugal
C Neves Portugal
E Nieschlag Germany
P Nilsson Sweden
K Norregaard Denmark
R Nogueiras Spain
A Norhammer Sweden
K Oberg Sweden
I Paiva Portugal
M Pfeifer Slovakia
D Pignatelli Italy
M Reinicke Germany
L Rejnmark Denmark
S Rhodes USA
F Rodrigues Portugal
E Rodrigues Portugal
J Romijn NL

P Roosing Denmark
M Sahin Turkey
L Savendahl Sweden
L Sechi Italy
J Silva Nunes
P Soares Portugal
A Spada Italy
M R Stimson UK
A Tabarin France
M Terus-Sempere Spain
M Thedoropoulou Germany
M Thichonirova Russia
J Tomlinson UK
J Toppari Finland
N B Tautunca Turkey
K Unhhinanci Turkey
A J van der Lely NL
J van Eck NL
A Vidal-Puig UK
T Vilsboell Denmark
S Virtue UK
J Visser NL
J M Wit NL
P Yeoh UK
M Zatelli Italy
C Zilnikens NL
SPONSORS
The ESE would like to thank the ECE 2013 sponsors

Gold Sponsors:
Ipsen
Novartis
Novo Nordisk
Pfizer

Bronze Sponsors:
Bayer Healthcare
Otsuka

ESE Office
Contact: Andrea Davis
Euro House
Tel: +44 (0)1454 642247
22 Apex Court
Fax: +44 (0)1454 642222
Woodlands
E-mail: info@euro-endo.org
Bradley Stoke
Web site: www.ese-hormones.org
Bristol BS32 4JT, UK

ECE 2013 Secretariat
Tel: +44 (0)1454 642240
BioScientifica Ltd
Fax: +44 (0)1454 642222
Euro House, 22 Apex Court
E-mail: ece2013@endocrinology.org
Woodlands
Website: http://www.ece2013.org
Bradley Stoke
Bristol BS32 4JT, UK

Endocrine Abstracts (2013) Vol 32
15th European Congress of Endocrinology 2013

**CONTENTS**

15th European Congress of Endocrinology 2013

**PRIZE LECTURES AND BIOGRAPHICAL NOTES**

- The European Journal of Endocrinology Prize Lecture ................................................. EJE1
- The Geoffrey Harris Prize Lecture ............................................................................. GH1

**PLENARY LECTURES**

- Nutrient-sensing pathways in ageing ................................................................. PL1
- NET Management .................................................................................................... PL2
- Changing character of thyroid cancer ..................................................................... PL3
- Fondation IPSEN 2013 Endocrine Regulations Prize ............................................ PL4
- Preventing vascular complications of diabetes .................................................... PL5
- The Ubiquitin System ............................................................................................... PL6
- New genes and functions in reproduction .............................................................. PL8
- Human Brown Fat is on Fire .................................................................................... PL9

**SYMPOSIA**

- Metabolic surgery .................................................................................................... S1.1–S1.3
- Cushing’s Disease with negative pituitary imaging ............................................. S2.1–S2.3
- Female reproduction ............................................................................................... S3.1–S3.3
- New advances in GPCRs in endocrinology .......................................................... S4.1–S4.3
- A guide through the labyrinth of neuroendocrine tumours ............................... S5.1–S5.3
- What’s new in type 2 diabetes? .............................................................................. S6.1–S6.3
- Translational aspects from comparative to clinical endocrinology ..................... S7.1–S7.3
- Action of glucocorticoids on bone .......................................................................... S8.1–S8.3
- New data treatment of hyperglycemia .................................................................... S9.1–S9.3
- Salt-water balance .................................................................................................. S10.1–S10.3
- New mechanisms in SST analogue response ...................................................... S11.1–S11.3
- Male reproductive endocrinology ......................................................................... S12.1–S12.3
- Hormonal treatment in transition of patients with rare diseases (Supported by the European Journal of Endocrinology) ................................ S13.1–S13.3
- Clinical care of the pheochromocytoma patient .................................................... S14.1–S14.3
- The Frail Male ......................................................................................................... S15.1–S15.3
- Oncogenic signals in thyroid cancer - therapeutic prospects .............................. S16.1–S16.3
- Medical treatment of endocrine malignancies - an update .................................. S17.1–S17.3
- PCOS ....................................................................................................................... S18.1–S18.3
- Recent advances in the molecular study of endocrine tumours: microRNAs and more  S19.1–S19.3
- New mechanisms of energy balance .................................................................... S20.1–S20.3
- Multi-centre pituitary studies ................................................................................ S21.1–S21.3
- Improving diagnosis of primary aldosteronism ............................................... S22.1–S22.3
- Endocrine disruptors (Supported by Endocrine Connections) ......................... S23.1–S23.3
- Redefining our understanding of the causes of obesity ....................................... S24.1–S24.3
- Rare metabolic bone disease ................................................................................ S25.1–S25.3
- Novel technologies and inspiring ideas: From basic endocrine research to clinical practice (European Young Endocrine Scientists (EYES) Symposium) .................. S26.1–S26.3
- Steroids in obesity and metabolism ...................................................................... S27.1–S27.3
- Autoimmune endocrine disease - Old and new players ...................................... S28.1–S28.3
- Management of thyroid nodules .......................................................................... S29.1–S29.3
Energy Status and pituitary function ............................................................. S30.1–S30.3
Clinical impact of rare mutations in endocrinology ..................................... S31.1–S31.3
Is diabetes a lipid disease? ............................................................................ S32.1–S32.3

MEET THE EXPERT SESSIONS ................................................................. MTE1–MTE16

JOE/JME PRIZE PRESENTATION Sponsored by Journal of Molecular Endocrinology
Enhancing radioiodine uptake in thyroid cancer ........................................... JP1

ENDOCRINE NURSING SYMPOSIUM ......................................................... EN1.1–EN3.5

ORAL COMMUNICATIONS
Pituitary & Molecular Endocrinology ........................................................... OC1.1–OC1.6
Bone & Calcium ............................................................................................ OC2.1–OC2.6
Thyroid ........................................................................................................... OC3.1–OC3.6
Adrenal ........................................................................................................... OC4.1–OC4.6
Reproduction ................................................................................................. OC5.1–OC5.6
Diabetes & Obesity ....................................................................................... OC6.1–OC6.6

NURSE POSTERS ....................................................................................... N1–N5

POSTER PRESENTATIONS
Adrenal cortex ................................................................................................. P1–P64
Adrenal Medulla .......................................................................................... P65–P69
Bone and Osteoporosis .............................................................................. P70–P110
Calcium and Vitamin D metabolism .......................................................... P111–P171.1
Cardiovascular Endocrinology & Lipid Metabolism .................................. P172–P212
Clinical case reports - Pituitary/Adrenal .................................................. P213–P269
Clinical case reports - Thyroid/Others ..................................................... P270–P331
Developmental Endocrinology ................................................................. P332–P345
Diabetes ........................................................................................................ P346–P496
Endocrine disruptors .................................................................................. P497–P507
Endocrine tumours and neoplasia .............................................................. P508–P573
Female reproduction ................................................................................ P574–P620
Growth hormone IGF axis - basic .............................................................. P621–P636
Male reproduction ...................................................................................... P637–P677
Neuroendocrinology .................................................................................. P678–P718.1
Nuclear receptors and signal transduction ............................................... P719–P725
Obesity .......................................................................................................... P726–P790
Paediatric endocrinology .......................................................................... P791–P822
Pituitary - Basic (Generously supported by IPSEN) .................................... P823–P839
Pituitary - Clinical (Generously supported by IPSEN) ................................ P840–P967
Steroid metabolism and action ................................................................ P968–P976
Thyroid (non-cancer) ................................................................................ P977–P1076
Thyroid cancer ........................................................................................... P1077–P1140

INDEX OF AUTHORS
Prize Lectures and Biographical Notes
The 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 on http://www.ese-hormones.org/prizes/eje.aspx. This year’s recipient is Professor Felix Beuschlein. The prize will be presented as part of the ECE 2013 opening ceremony where Prof. Beuschlein will deliver his lecture. Prof. Beuschlein has also written a review article based on this lecture that has been accepted for publication in the European Journal of Endocrinology and can be accessed at DOI:10.1530/EJE-13-0263.

Felix Beuschlein, Germany

Felix Beuschlein was born in 1969 and went to medical school at the University of Würzburg. For his doctoral thesis he worked on projects related to adrenal tumorigenesis. This field of expertise was further intensified during a postdoctoral fellowship under the mentorship of Gary Hammer at the University of Michigan where he utilized a number of mouse models to elucidate mechanisms of adrenal growth and steroidogenesis. Upon his return to Germany at the University Hospital in Freiburg he established his own group on adrenal stem cell research and completed his medical training. In 2006, he became a full professor as the head of Endocrine Research at the University in Munich. Prof Beuschlein has received a number of awards including the Marius-Tausk and Schöller-Junkmann award from the German Endocrine Society as well as the Merck Senior Fellow Award by the Endocrine Society. He serves as the vice-president of the German Endocrine Society, as a board member of the Research Affairs Core Committee of the Endocrine Society and the executive committee of Pressor. He is the chairman of the European Network for the Study of Adrenal Tumors (ENSAT) and coordinator of an FP7 consortium.
Regulation of aldosterone secretion: from physiology to disease

Felix Beuschlein, University Clinic Munich, Munich, Germany

Arterial hypertension is a major cardiovascular risk factor that affects between 10 and 40% of the population in industrialized countries. Primary aldosteronism (PA) is the most common form of secondary hypertension with an estimated prevalence of ~10% in referred patients and 4% in primary care. Despite its high prevalence until recently the underlying genetic and molecular basis of this common disease has remained largely obscure with the exception of the small subgroup of patients with familial hyperaldosteronism type I.

Over the past decade a number of insights have been achieved that rely on in vitro cellular systems, wild-type and genetically modified in vivo models as well as pre-clinical and clinical studies in well-characterized patient populations. This progress has been made possible by a number of independent technical developments including that of specific hormone assays that allow measurement in small sample volumes as well as genetic techniques that enable high throughput sequencing of a large number of samples. Furthermore, animal models have provided important insights in the physiology of aldosterone regulation that have served as a starting point for investigation of mechanisms involved in autonomous aldosterone secretion. Finally, national and international networks that have built up registries and biobanks have been instrumental to foster translational research endeavors in PA.

Recently, a number of approaches including genome wide association studies, exome sequencing and mutagenesis screens have been applied in patient cohorts and in vivo models of PA. Thereby, it is to be expected that in the near future further pathophysiological mechanisms that result in autonomous aldosterone secretion will be unraveled.
The Geoffrey Harris Prize Winner

Professor Clarke graduated from Massey University, New Zealand (B. Agric. Sci., 1971) followed by M. Agric. Sci. (1st Class) in reproductive physiology in 1973). He then obtained his PhD at Edinburgh University, Scotland in 1976, studying endocrinology and behaviour. He has since moved to Australia and became Senior Research Fellow of NHMRC in 1986, rising to Principal Research Fellow in 1991. He became Chairman, Department of Physiology, Monash University in 2007. Prof. Clarke’s seminal studies on the measurement of hypothalamic secretion of GnRH in sentient animals were published in 1982 and he has contributed extensively to the field of reproductive neuro endocrinology for 35 years. His laboratory currently focuses on Central regulation of reproduction by kisspeptin and gonadotropin inhibitory hormone; estrogen signalling in neuroendocrine systems; control of food intake and energy expenditure by leptin and novel regulatory factors; melanocortins and reproduction; central regulation of energy expenditure.

Prof. Clarke has published 430 research papers and has received The Woodward Prize for Excellence in Research in Neuroscience (1992), a Senior Fulbright Award (1997), the Asia and Oceania Medal of Society for Endocrinology (UK) in 2001 and the TransPacific Lecturership, Endocrine Society (USA) in 2004. Most recently (2009), he was the recipient of The Geoffrey Harris Memorial Award of the International Federation of Neuroendocrinology (2009).
The Geoffrey Harris Prize Lecture

Speakers, cross-talk and chatter in reproductive neuroendocrinology

Iain Clarke, Department of Physiology, Monash University, Victoria, Melbourne, Australia

The brain controls reproduction through the secretion of GnRH, but a series of higher brain centres control the secretion of GnRH into the hypophysial portal system. Whereas GnRH might be considered the ‘speaker’ for the brain in the reproductive axis, there is significant ‘cross-talk and chatter’ relating to the higher brain centres of control. Most prominently, kisspeptin mediates the feedback effect of sex steroids on GnRH cells, which may be effected at the level of the GnRH cell bodies or the secretory terminals in the median eminence. Gonadotropin inhibitory hormone (GnIH) has also emerged as a major negative regulator of GnRH secretion and action, acting on the GnRH neurons but also being secreted into the hypophysial portal system to act on the pituitary gonadotropes. This provides ‘cross-talk’ and data will be reviewed for GnIH function in mammals. The ‘chatter’ within this system involves input from centres within the brain that respond to altered nutritional status/metabolic condition, season and stress. Alterations in energy balance change the activity of appetite regulating peptide neurons in the hypothalamus. These neurons interact with kisspeptin cells, leading to changes in GnRH secretion. Season also involves changes in kisspeptin function as well as GnIH secretion. Stress has a negative impact on the reproductive neuroendocrine system and very recent data show that this involves upregulation of GnIH gene expression. In essence, GnRH neurons are controlled by serial and converging neuronal inputs from various brain centres. The same appears to be true for GnIH neurons, so the combined output of GnRH and GnIH dictates reproductive function.
Plenary Lectures
Nutrient-sensing pathways in ageing

PL1

Nutrient-sensing pathways and ageing

Linda Partridge1,2
1Max Planck Institute for Biology of Ageing, Cologne, Germany;
2University College London, London, UK.

Research into ageing has been transformed by the discovery of single gene mutations that extend healthy lifespan in laboratory model organisms. Furthermore, the highly conserved, nutrient-sensing, insulin/IGF/TOR signalling network has proved to play a role in ageing in organisms including yeast, invertebrates and mice, and possibly also humans. This signalling network also mediates at least some of the effects of dietary restriction, which also improves health during ageing and extends lifespan in diverse organisms including rhesus monkeys. These interventions can protect against diverse ageing-related loss of function and disease, raising the prospect of the broad-spectrum, preventative medicine for ageing-related disease.

Less well understood are the biochemical mechanisms by which reduced activity of this nutrient-sensing network can improve health during ageing, and the types of ageing-related damage that are ameliorated. For instance, toxic endo- and xenobiotics can be sources of damage. One hypothesis is that the ameliorated ability to metabolize toxic compounds leads to the life span extension. The nuclear hormone receptor DHR96 is a target gene of a key component of the signalling network; it is also involved in xenobiotic metabolism. Manipulation of hormone nuclear receptors in the fly could shed light on this.

Given the highly pleiotropic effects of this signalling network, understanding its role in ageing is crucial for identifying potential drug targets to minimise health benefits with minimal side-effects.

DOI: 10.1530/endoabs.32.PL1

NET Management

PL2

Neuroendocrine tumour management

Lisa Bodei & Giovanni Paganelli
Division of nuclear medicine of the European Institute of Oncology, Milan, Italy.

Neuroendocrine tumours (NETs) tend to be slow growing (although aggressive forms exist) and are often diagnosed when they have already metastasised.

Treatment of NETs is typically multidisciplinary and should be individualised according to the tumour type, burden, and symptoms. Therapeutic tools in NETs include surgery, interventional radiology and medical treatments such as somatostatin analogues, interferon, chemotherapy, new targeted drugs and peptide receptor radionuclide therapy (PRRT) with radiolabelled somatostatin analogues.

Surgery is crucial in many phases, from the eradication of the primary to the debulking of metastatic lesions, especially in a multidisciplinary algorithm. It is also used to control hormonal symptoms.

Interventional radiology techniques (TACE, RFA, and radioembolization) in NETs are frequently used, due to the common spread to the liver with hypervascular metastases.

Medical therapy is used for treating symptoms and/or reducing tumour growth. Traditional chemotherapy is not commonly applied in G1–G2 NETs, since most of them are slow growing. However, schemes based on platinum derivatives and etoposide are considered in poorly differentiated and/or rapidly progressive NETs, but the choice of the regimen is based on the site of the primary, the histopathological differentiation and proliferation index.

NETs usually over-express somatostatin receptors on their cell surface, thus enabling the therapeutic use of somatostatin analogues to reduce signs and symptoms of hormone hypersecretion, to improve quality of life and to slow the tumour growth.

Interferon has been used in NETs, with similar therapeutic effects.

Recently, the mTOR inhibitor everolimus and the tyrosine kinase inhibitor sunitinib demonstrated an impact on survival parameters in patients with pancreatic NETs and have been introduced in clinical practice. The anti-VEGF monoclonal antibody bevacizumab demonstrated an impact on survival parameters in patient with metastatic carcinoids.

Radiolabelled somatostatin analogues have been experimented in NETs for almost two decades. Several clinical trials have indicated that PRRT with 111In-DOTATOC and 90Y-DOTATATE is an efficient tool in the management of NETs. Pretreatment knowledge and clinical experience indicate that it is possible to deliver high activities, and therefore high absorbed doses, to targets expressing sst receptors, with achievement of partial and complete objective therapeutic responses in up to 30% of patients with PFS of 33–36 months and a consistent impact on survival. Side effects, involving the kidney and the bone marrow, are mild if adequate renal protection is used.

DOI: 10.1530/endoabs.32.PL2

Changing character of thyroid cancer

PL3

Changing character of thyroid cancer

Maria Alevizaki
Athens University School of Medicine, Athens, Greece.

Thyroid cancer (DTC) is diagnosed more frequently these days due to increased awareness, wider availability of detection tools and, possibly, to true increasing incidence. The epidemiology of DTC is thus changing and more ‘innocent’ tumours are now being detected. The management of thyroid cancer and nodules is evolving and much progress has recently been made in the diagnosis and follow-up. Management guidelines have recently been published by scientific bodies and are continuously revised incorporating the accumulating new data.

The most important changes have been made in the management of these patients, where in the past a uniform approach was used almost regardless of risk factors for recurrence. The use of lower radiiodine doses (RAI) for remnant ablation and different strategies to increase RAI uptake have been examined in randomized clinical trials and have provided useful information that may now be used in practice. Measurement of stimulated thyroglobulin (either with endogenous or exogenous TSH) and high resolution ultrasound are valuable tools used to evaluate the success of intervention and assess the probability of cure.

Furthermore, individualisation of care is supported from data about the excellent prognosis in the majority of cases. The current, ‘modern day’, approach involves the reassessment of risk of recurrence at regular intervals during follow up incorporating the response to treatment. The aim of such strategy is to identify the few cases that are at higher risk and modify the intensity of re-evaluation in the others. Thus the ‘optimal’ management of thyroid cancer patients is currently the focus of research to assure that patients will not be over-treated or over-followed up, such that they may have fewer complications and side effects and less psychological burden.

DOI: 10.1530/endoabs.32.PL3

Fondation IPSEN 2013 Endocrine Regulations Prize

PL4

Nuclear receptor ‘master’ coactivators of physiology and pathology

Bert O’Malley
Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, Texas, USA.

Nuclear receptors control gene expression by recruiting transcriptional coactivators (or corepressors). The coactivators are ‘master regulators’ that coordinately activate multiple distinct transcription factors and target genes and pathways to control major physiologic processes such as reproduction, inflammation, metabolism and growth. Because of their central role as ‘nodes’ of regulation, coactivators are major targets in the development of numerous inherited and acquired endocrine-related pathologies such as infertility, endometriosis, disorders of carbohydrate, lipid and protein metabolism, and numerous cancers. Metabolism and growth are especially prominent pathways for coordinate regulation by coactivators such as SRC-2 and SRC-3. The pleiotropic functions of coactivators in pathways are the result of combinatorial posttranslational modifications of the proteins via enzyme cascades, in conjunction with certain biological isoforms of the proteins. In metabolic diseases and cancers, the intracellular concentrations and the PTM-directed ‘activities’ of the coactivator proteins are critical for ‘driving’ the transcription-dependent physiological outcomes. However, in the case of the cancer cell’s motility or in endometriosis, it is the coactivator protein’s isoforms that are the major mediators of the disease progression. Thus, as a class, the coactivator proteins provide important insights to polygenic diseases. They also may
represent new ‘first-in-class’ types of potential targets for therapeutic intervention.

DOI: 10.1530/endoabs.32.PL4

Preventing vascular complications of diabetes

PL5

Prevention and treatment of renal and cardiovascular disease in diabetes: new aspects
Hans-Henrik Parving
Department of Medical Endocrinology, National University Hospital, Copenhagen, Denmark.

The activity of the renin-angiotensin system (RAAS) is elevated in the circulation and in various tissues and organ tissues. The increased RAAS activity plays an important role in the haemodynamic and non-haemodynamic pathogenetic mechanisms involved in kidney and vascular (CV) disease. Previous studies have demonstrated that albuminuria is not only a marker of glomerular lesions but also a progression promoter and finally a powerful predictor of the long term beneficial effect of blood pressure lowering therapy. Furthermore albuminuria is a harbinger of CV disease. Randomized blinded studies of patients with diabetic nephropathy have demonstrated:

- Angiotensin II receptor blockers (ARB) can prevent/delay development of microalbuminuria and diabetic nephropathy independently of its beneficial blood lowering effect in hypertensive patients with type 2 diabetes and normoalbuminuria/microalbuminuria (BENEDICT and IRMA 2)
- Early ARB treatment is projected to improve life expectancy and reduce cost in hypertensive patients with type 2 diabetes and microalbuminuria. Later use of ARB in overt nephropathy is also superior to standard care, but ARB should be started earlier and continued long term.
- Two landmark studies (RENAAL and IDNT) lead to the following conclusion: ‘Losartan and Irbesartan confered significant renal benefit in patients with type 2 diabetes and nephropathy. This protection is independent of the reduction in blood pressure it causes. The ARB is generally safe and well-tolerated’.
- Albuminuria is an important factor predicting cardiovascular risk in patients with type 2 diabetic nephropathy. Reducing albuminuria with ARB in the first 6 months appears to afford cardiovascular protection in these patients.
- The antiproteinuric effect of ARB explains a large part of the specific renoprotective characteristic. Proteinuria should be considered a risk marker for progressive renal function loss in type 2 diabetes with nephropathy, as well as target for therapy. Lowering of residual proteinuria is a goal for the future.
- Recent studies suggest that remission of nephrotic range albuminuria induced by aggressive antihypertensive treatment is associated with a slower progression in diabetic nephropathy and a substantial improved survival.
- Recent studies have suggested new renoprotective treatment modalities, e.g. ultrahigh dose of RAAS-blockade, combination of ACEI and ARB; aldosterone blockers and direct renin inhibition.

Intensified multifactorial intervention – with tight glucose regulation and the use of renin-angiotensin system blockers, aspirin, and lipid-lowering agents – has been shown to reduce the risk of nonfatal cardiovascular disease among patients with type 2 diabetes mellitus and microalbuminuria. We evaluated whether this approach would have an effect on the rates of death from any cause and from cardiovascular causes.

In the Steno-2 study we randomly assigned 160 patients with type 2 diabetes and persistent microalbuminuria to receive either intensive therapy or conventional therapy; the mean treatment period was 7.8 years. Patients were subsequently followed observationally for a mean of 5.5 years until December 31, 2006. The primary end point at 13.3 years of follow-up was the time of death from any cause. Twenty-four patients in the intensive-therapy group died, as compared with 40 in the control group (hazard ratio, 0.43; 95% CI, 0.19 to 0.94; P = 0.02). Intensive therapy was associated with lower risk of death from cardiovascular causes (hazard ratio, 0.43; 95% CI, 0.19 to 0.94; P = 0.04) and of cardiovascular events (hazard ratio, 0.41; 95% CI, 0.25 to 0.67; P < 0.001). One patient in the intensive-therapy group had progression to end-stage renal disease, as compared with six patients in the conventional-therapy group (P = 0.04). Fewer patients in the intensive-therapy group required retinal photocoagulation (relative risk, 0.45; 95% CI, 0.23 to 0.86; P = 0.02). Few major side effects were reported.

In at-risk patients with type 2 diabetes, intensive intervention with multiple drug combinations and behaviour modification has sustained beneficial effects with respect to vascular complications and on rates of death from any cause and from cardiovascular causes.

DOI: 10.1530/endoabs.32.PL5

The Ubiquitin System

PL6

Abstract unavailable.

DOI: 10.1530/endoabs.32.PL6

Aldosterone, Mineralocorticoid Receptors and Cardiovascular Risk: What’s New?

PL7

Aldosterone, mineralocorticoid receptors and cardiovascular risk: what’s new?
J Funder
Prince Henry’s Institute, Monash Medical Centre, Clayton, Victoria, Australia.

Classically aldosterone acted uniquely on epithelia, and primary aldosteronism (PA) was considered uncommon and relatively benign, all of which we now know to be not the case. In 2013, we should note that:

i). Mineralocorticoid receptors (MR) evolved millions of years before aldosterone.
ii). Cortisol occupies 90–99% of all MR in the human body.
iii). MR are promiscuous, binding cortisol, aldosterone and progesterone with the same high affinity.
iv). Cortisol is bivalent: normally an antagonist of aldosterone in MR, it acts as an agonist under conditions of tissue damage/reactive oxygen species generation/redox change.
v). Cortisol is thus the cardiac/vascular MR agonist in essential hypertension (EH) and congestive heart failure (CHF).
vi). Spironolactone and eplerenone do not act primarily by denying agonist access to MR, but as inverse agonists in their own right.

vii). Around 40% of PA due to an aldosterone producing adenoma is due to somatic mutation of KCNJ5, with further somatic mutations in press.

viii). Three germ line mutations causing PA have been distinguished: Familial Hyperaldosteronism Type 1 and 3 are rare (<1%), but the prevalence of FH2 is likely to be much higher.
ix). The currently accepted prevalence of PA may be too low, and the upper limit of ‘normal’ aldosterone too high, with evidence accruing that many patients with resistant hypertension and low renin hypertension have autonomous aldosterone secretion, i.e. PA.

x). Even at currently accepted levels for PA fewer than I% of patients are ever screened, diagnosed and specifically treated.

xi). No jurisdiction has the resources – financial or medical – to meaningfully raise this percentage.

xii). Low dose MR antagonists are safe and efficacious in EH, selectively active in resistant hypertension, and game-changing in PA; and so.

xiii). Given the much higher cardiovascular risk profile of PA than in age-, sex- and blood pressure-matched EH, and that 99-1% of PA remains occult, low dose MR antagonists should be included in first-line therapy for all hypertensives.

DOI: 10.1530/endoabs.32.PL7

New genes and functions in reproduction

PL8

New genes and functions in reproduction
Martin M Matzuk
Department of Pathology and Immunology, Baylor College of Medicine, Houston, Texas, USA.

For almost three decades, my group and I have been studying the functions of known proteins and deciphering the roles of novel genes and small RNAs expressed within the reproductive axis. Many of these studies have focused on the glycoprotein hormones as well as members of the transforming growth factor β superfamily. We have also used multiple strategies to identify unique germ-cell
expressed genes and probed their essential roles in knockout mouse models. These studies have led us to an understanding of the intricate pathways required for development and function of the reproductive axis in mammals.

DOI: 10.1530/endoabs.32.PL8

Human Brown Fat is on Fire
PL9

Human brown fat is on fire
Barbara Cannon
Wenner-Gren Institute, Stockholm, Sweden.

Brown adipose tissue was classically a tissue with scientifically interesting bioenergetic features, manifest by the unique presence of uncoupling protein-1 in only this tissue – but it was considered to have no metabolic significance for adult humans. The acceptance within the last years of its presence in adult humans has intensified interest in its potential ability not only to keep us warm but particularly to burn excess energy, i.e. to keep us slim, and – through its utilization of lipids and glucose – to counteract the metabolic syndrome. The analysis of its function and significance in experimental animals can now likely be extrapolated to humans. The principal conclusion is that brown adipose tissue is the sole organ responsible for classical nonshivering thermogenesis as well as for diet-induced thermogenesis, and that no other mechanisms for adaptive thermogenesis exists. The extrapolation is evidently that its activity potentially could be exploited to promote human health.

DOI: 10.1530/endoabs.32.PL9
Symposia
Metabolic surgery

S1.1

New insights in obesity pathophysiology of metabolic surgery

Gema Frühbeck1,2

1Department of Endocrinology and Nutrition, Clinica Univ. de Navarra, University of Navarra, Pamplona, Spain. 2CIBERObn, Instituto de Salud Carlos III, Pamplona, Spain.

Obesity represents an important risk factor for type 2 diabetes mellitus (T2DM) development. The outcomes of both bariatric and metabolic surgery have provided new insights into the mechanisms responsible for body weight control and glucose homeostasis. However, at the same time the marked effects of metabolic surgery on T2DM highlights the limitations of our current knowledge underscoring the need to continue addressing relevant questions as regards the underlying mechanisms and their precise contribution in each case. As expected, weight loss improves the major factors involved in the pathogenesis of T2DM, namely insulin action and β cell function. Interestingly, over the past decades bariatric surgical procedures that divert nutrients away from the upper gastrointestinal system are more successful in producing weight loss and remission of T2DM than those that simply restrict stomach capacity. Moreover, the almost immediate beneficial effects on glucose homeostasis following bariatric surgery when no substantial change in body weight has taken place points to the existence of relevant weight loss-independent factors. This statement is based primarily on the following findings: i) the early postoperative effects of especially some types of bariatric surgery on glycemic control; ii) the long-term efficacy of different surgical procedures on T2DM resolution; iii) the effect of the duodenal-jejunal bypass (DJB), which greatly influences glucose homeostasis despite minimal weight loss; and iv) the rapid and specific hormonal response to glucose or mixed meal ingestion. Circulating insulin levels represent a summation of events that involve both β cell and non-β cell metabolic pathways. Furthermore, BMI and total body weight do not reflect differences in body composition and adiposity distribution, thereby ignoring the relationship between the different compartments (fat, muscle, liver, etc.) and metabolic risk. More research is needed to make definitive conclusions on the precise and probably multifactorial causes backing metabolic surgery effectiveness.

DOI: 10.1530/endoabs.32.S1.1

S1.2

Abstract unavailable.

DOI: 10.1530/endoabs.32.S1.2

S1.3

Abstract unavailable.

DOI: 10.1530/endoabs.32.S1.3

Cushing’s Disease with negative pituitary imaging

S2.1

Abstract unavailable.

DOI: 10.1530/endoabs.32.S2.1

S2.2

Surgical approach to corticotroph adenomas poorly visible at preoperative imaging

Michael Buchfelder

Department of Neurosurgery, University of Erlangen-Nürnberg, Erlangen, Germany.

Most pituitary operations for Cushing’s disease are technically difficult procedures. Since the source of excessive ACTH-secretion in Cushing’s disease is almost invariably a pituitary microadenoma, selective resection of this minute tumor is considered the primary standard therapy. However, almost half of the tumors escape direct preoperative detection even by sophisticated magnetic resonance imaging. Thus, in these the indication for surgery is based on laboratory findings of hormone determinations, including dynamic tests and selective blood sampling from the inferior petrosal sinus. Systematic sectioning of the gland is required to find the tiny tumor. Technical supports, like intraoperative sonography, have been introduced. Following successful surgery, ACTH and cortisol levels, respectively, decrease rapidly to ideally reach subnormal levels. Such an isolated adenocortical insufficiency is a favourable prognostic indicator for long-lasting remission and requires corticosteroid substitution. Some 65–90% of patients harbouring pituitary microadenomas experience a remission after transsphenoidal pituitary surgery in experienced centers. In most series, negative imaging is an unfavourable prognostic factor. Moreover, there is a recurrence rate of some 10–20% at 10 years. Also the technical performance of such transsphenoidal sella explorations is challenging. The sella is frequently normal sized, incompletely pneumatized and thus, more venous bleeding occurs intraoperatively than with larger adenomas. Many of the patients harbour significant comorbidities. However, in some 90% of patients microadenomas are detected intra-operatively. Not in all of these, representative tissue arrives in the pathologist’s laboratory. For ill-defined tumors, lateral hemihypophysectomy, central core partial hypophysectomy or total hypophysectomy may be considered. However, the success rate of any kind of hypophysectomy in terms of normal ACTH- and cortisol secretion is lower than that of selective operations in patients with distinct radiological findings.

DOI: 10.1530/endoabs.32.S2.2

S2.3

Medical approach to Cushing’s disease: results of a French multicentre study

Frederic Castinetti

Department of Endocrinology and Reference Center for Rare Pituitary Diseases, La Timone Hospital, Aix Marseille University, Marseille, France.

Surgery remains the first line treatment of Cushing’s disease. However, recent studies based on long term follow-up showed that the risk of late recurrence was close to 20–30% cases, whatever the immediate post-surgical cortisol level. In other cases, surgery is not possible due to contra-indications, or refusal by the patient. Medical treatment is thus of major importance in the management of Cushing’s disease, also taking into account the delay to obtain maximal efficacy of radiation techniques, when they are indicated. This talk will be aimed at showing the main merits and pitfalls of anticortisolic drugs, first by evaluating the recently used new pituitary targeted drugs, and then by comparing them to the classical adrenal targeted anticortisolic drugs. Among these, ketoconazole should be considered as a valuable treatment. Despite a relatively low number of cases reported to date, this drug has been shown to be effective and relatively safe. We will present here the results of a French multicentric retrospective study based on more than 150 patients treated by ketoconazole for Cushing’s disease, and will try to define its role in the therapeutic algorithm of this disease.

DOI: 10.1530/endoabs.32.S2.3

Female reproduction

S3.1

The transcription factor FOXL2 in ovarian physiology and pathology

Reiner Veitia

Université Paris Diderot/IBM, Paris, France.

The gene FOXL2 encodes a forkhead transcription factor whose mutations or misregulation are responsible for the blepharophimosis-ptosis-epicanthus
New advances in GPCRs in endocrinology

**S4.1**

**Biased agonism of the AT1 receptor: perspectives in drug discovery?**

J H Hansen
Novo Nordisk A/S, Diabetes Biology, Denmark.

The angiotensin II type 1 receptor (AT1R) belongs to the family of seven transmembrane (7TM) receptors, also referred to as G-protein coupled receptors. The AT1R is the primary effector of the renin–angiotensin system, and serves as a key regulator of cardiovascular physiology. The importance of the receptor is clearly illustrated be the frequent use of AT1R blockers and ACE inhibitors in cardiovascular medicine. Upon binding of Ang II the AT1R is signals through both G protein-dependent and -independent pathways. The G protein-dependent pathways are well established and studied in detail whereas we know less about G protein-independent pathways. Pharmacological targeted activation and blocking of the signaling cascades provides novel tools to increase the understanding of how these receptors exert their cellular functions and importantly it present a new clinical potential. This so-called biased agonism (or functional selectivity) has been studied extensively for the last decade and the focus is still increasing. In this talk I will introduce the concept of AT1R mediated biased agonism, discuss the underlying complexity of the AT1R signaling transduction networks and gene regulation and present the clinical potential of AT1R biased agonists.

DOI: 10.1530/endoabs.32.S4.2

**S4.3**

**G-protein-coupled receptor heteromers as new targets for drug development**

Rafael Franco1,2
Centro de Investigación Médica Aplicada, Pamplona, Navarra, Spain; Depto. Biosquimica i Biologia Molecular, Barcelona, Catalonia, Spain.

Together with Profs Lefkowitz and Kohilkia, G-protein-coupled receptors (GPCRs) have taken the stage in the 2012 Nobel award for Chemistry. The Royal Swedish Academy of Sciences states that ‘About half of all medications achieve their effect through G-protein-coupled receptors’. As shown in previous papers, the GPCR field is continuously developing and fascinating. On the ground of the fact that GPCRs are not acting individually, often they form homodimers and, more interestingly, they may occur as heterodimers. Heteromers open a completely new scenario for structural and functional diversity and for drug discovery. As a result, GPCR heteromers are being studied extensively for their role in the regulation of female reproductive behavior. This lack of information about the brain functions of PR is an unexpected, as progesterone is known to exert multiple effects on neural cells. Moreover, the neuroprotective effects of progesterone have been extensively studied for their role in the regulation of female reproductive behavior. It is indeed widely acknowledged that progesterone has anxiolytic, anesthetic and anticonvulsant properties. The elucidation of the impact of FOXL2 germline and somatic mutations will ensure a better understanding of the pathogenesis of BPES and of OGCTs.

DOI: 10.1530/endoabs.32.S3.1
A guide through the labyrinth of neuroendocrine tumours

S5.1 Tumor biology and classification of NET
Aldo Scarpa
University of Verona, Verona, Italy.

Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) constitute a heterogenous group of neoplasms. In the last few decades, due to a substantial rise in incidence and prevalence, GEP-NETs have been included among the most common tumors of the gastrointestinal tract. Diagnosis could be challenging and a significant number of patients present with metastatic or unresectable disease. The development of appropriate tools for standardized prognostic stratification and the introduction of effective target therapies have opened new horizons for planning tailored surgical or medical management and follow-up programs for these complex neoplasms. An overview on the GEP-NETs’ diagnostic and prognostic criteria proposed by the recently published WHO classification and ENETS and UICC TNM staging systems is presented, focusing on their impact on the clinical and therapeutical approaches.

The genetic events underlying the tumorigenesis of this complex group of neoplasms still remain to be defined. Very recently, extensive investigations have focused on the neuroendocrine tumors of pancreatic origin (PEN). Indeed, massive-scale sequencing PEN has led to the identification of alterations of genes involved in the chromatin remoulding (MEN1, DAXX, and ATRX) in up to 60% of cases. Moreover, a small subgroup of patients harbored alterations in genes (PTEN and TSC2) that negatively regulate mTOR activation, for which targeted therapy in PEN already exist. Beyond alterations in protein coding genes, survey of chromosomal status have demonstrated that a high degree of genomic instability correlates with the aggressiveness of this neoplasm. Gene silencing by promoter methylation has been advocated, but a formal demonstration of the involvement of specific genes is still lacking. Expression profiling studies are furnishing valuable lists of mRNAs and noncoding RNAs that may advance further the research to discover novel markers and/or therapeutic targets.

DOI: 10.1530/endoabs.32.S5.1

S5.2 Nuclear medicine imaging of neuroendocrine tumours
Anders Sundin1,2
1Karolinska University Hospital, Stockholm, Sweden; 2Karolinska Institute, Stockholm, Sweden.

Computed tomography (CT) is the basic method for morphological imaging of neuroendocrine tumours (NETs) for visualization of local tumour extent and staging of regional and distant metastases. Magnetic resonance imaging (MRI) and intravenously contrast-enhanced ultrasound (CEUS) are complementary methods but are less frequently available and are therefore predominately used when CT does not suffice. This, however, varies depending on the local situation and expertise. Endoscopic US (EUS) is superior for detection and to evaluate the local extent of gastric, duodenal and pancreatic NETs but has similarly limited availability.

Scintigraphy by 111In-labelled octreotide (OctreoScan) remains the mainstay for evaluation of the NET’s somatostatin receptor status and generally facilitates tumour staging and is important to assess the patient’s eligibility for treatment with somatostatin analogues. Recently, various 68Ga-labelled somatostatin analogues have been tested for NET imaging by positron emission tomography (PET) in combination with CT (PET/CT). Generally, 68Ga-labelled octreotide (68Ga-DOTA-TOC, 68Ga-DOTA-NOC) and octreotate (68Ga-DOTA-TATE) are used as PET tracers. Somatostatin receptor imaging by PET has in several comparative studies performed better than scintigraphy. Centres where PET/CT with 68Ga-labelled somatostatin analogues is available are still few but the technique is fairly rapidly increasing and scintigraphy with OctreoScan has in these centres generally been abandoned. Because of existing protocols, scintigraphy with OctreoScan is still performed for patient selection when peptide receptor radio therapy (PRRT) with 177Lu-DOTA-TATE is considered. Because of the 68Ga-labelled somatostatin analogue preparations favourable pharmacokinetics, PET imaging can be performed already 30–60 min after tracer injection as compared to scintigraphy, which is generally performed at 4 and 24 h. Also the spatial resolution of PET and the image contrast is better.

DOI: 10.1530/endoabs.32.S5.2

S6.1 The impact of our genomes on metabolic health
Torben Hansen
The Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, Copenhagen, Denmark.

For the past two decades, genetics has been widely explored as a tool for unravelling the pathogenesis of cardio-metabolic disorders. Many risk alleles for type 2 diabetes and hyperglycaemia have been detected in recent years through massive genome-wide association studies and evidence exists that most of these variants influence pancreatic β-cell function. Investigations of more detailed physiological phenotypes, are now emerging and give indications of more specific pathological mechanism for diabetes-related risk variants. Such studies have shed light on the function of some loci but also underlined the complex nature of disease mechanism. In the future, sequencing-based discovery of low-frequency variants with higher impact on intermediate diabetes-related traits is a likely scenario and identification of new pathways involved in type 2 diabetes predisposition will offer opportunities for the development of novel therapeutic and preventative approaches. Furthermore, we recently described the Illumina-based metagenomic sequencing assembly and characterisation of 3.3 million non-redundant microbial genes from faecal samples of 124 European individuals. The extensive gene catalogue has enabled us to perform studies of association of the microbial genes with human metabolic phenotypes.

DOI: 10.1530/endoabs.32.S6.1

Endocrine Abstracts (2013) Vol 32
Inability to store excess lipids in the subcutaneous adipose tissue leads to ectopic lipid deposition in several sites including the liver, skeletal muscles, intra-abdominal and pericardial depots. This, in turn, has negative consequences for degree of insulin sensitivity and the dysmetabolic state associated with insulin resistance and type 2 diabetes.

Storage of fat in the adipose tissue can either lead to inappropriate cellular enlargement (hypertrophic obesity) or the recruitment of new adipose cells (hydroplastic obesity). The latter is more favourable from a metabolic point of view and is associated with the ‘obese but metabolically normal’ phenotype. The reason for this difference in storing excess lipids is related to an ability or not to recruit and differentiate new adipose cells from precursor cells. We have in a series of papers shown that hypertrophic obesity is associated with insulin resistant adipose tissue with reduced expression of IRS1, GLUT4 and several other PPARγ-regulated genes and occurred around four times more frequently in individuals with a genetic predisposition for type 2 diabetes (first degree relatives, FDR) than in individuals lacking a genetic predisposition. In recent studies, we have found that FDR exhibit an obese metabolic phenotype with inappropriately enlarged adipose cells, reduced insulin sensitivity and a dysregulated adipose tissue even in the absence of obesity while this phenotype is not found in subjects with heredity for obesity/overweight. These findings provide a link between diabetes heredity and increased sensitivity to the environment and caloric excess. Furthermore, we have recently identified a novel mechanism whereby mesenchymal stem cells and other precursor cells become committed to the adipose lineage in response to BMP4 and subsequently can undergo differentiation.

DOI: 10.1530/endoabs.32.S6.2

**S6.3**

**Mechanisms of β cell failure in type 2 diabetes**

Miriam Cnop

Division of Endocrinology, Laboratory of Experimental Medicine, Erasmus Hospital, Université Libre de Bruxelles, Brussels, Belgium.

Pancreatic β cell dysfunction and death are central in the pathogenesis of type 2 diabetes but the underlying mechanisms are not well understood. Genetic factors predispose to type 2 diabetes but, despite very large scale genome-wide association studies, the heritability of the disease remains largely unexplained. Environmental and lifestyle factors contribute to the pathogenesis of type 2 diabetes and likely explain its rapidly increasing prevalence. Elevated levels of saturated free fatty acids may cause β cell failure in insulin resistant individuals, and our work aims to clarify the molecular mechanisms involved. Epigenetic changes are an additional link for translating environmental exposures into heritable disease mechanisms. Human β cells are long-lived, and have a lifetime to acquire epigenetic alterations.

We have performed the first comprehensive DNA methylation profiling in human islets from type 2 diabetic and non-diabetic donors, identifying differential DNA methylation in genes in pathways affecting β cell function and survival. In parallel, we are mapping the human islet transcriptome by RNA-sequencing, under control condition or following exposure to the saturated fatty acid palmitate. Palmitate modified transcripts related to the endoplasmic reticulum stress response, ubiquitin and proteasome function, autophagy and apoptosis. Several transcription factors controlling β cell phenotype were inhibited by palmitate. In addition, palmitate caused a shift in alternative splicing, pointing to novel mechanisms of palmitate-induced β cell dysfunction and death. These omic approaches will offer new insights into the pathogenesis of diabetes. A better understanding of the epigenetic dysregulation in type 2 diabetic islets and the mapping of the human islet transcriptome will advance our understanding of disease etiology.

DOI: 10.1530/endoabs.32.S6.3

**Translational aspects from comparative to clinical endocrinology**

**S7.1**

**Brain aromatase and endocrine disruptors in zebrafish: from basic to applied research**

O Kah

Research Institute in Health, Environment and Occupation, Team NEED, Université de Rennes, France.

Aromatase is the only enzyme converting androgens into estrogens, which are key actors in reproductive biology. Teleost fishes have two copies of the cyp19a1 gene, which encode two isoforms of aromatase: cyp19a1a encodes ovarian aromatase, while the cyp19a1b gene encodes brain aromatase. Our recent work showed that, in zebrafish, aromatase B is strongly expressed in a unique brain cell type, the radial glial cells (RGC). In mammals, such cells act as stem cells during embryonic development before disappearing in adults. On the contrary, in fishes, RGCs persist in adult where they act as neuronal progenitors allowing the brain to constantly keep growing. We have also shown that, intriguingly, the cyp19a1b gene is very sensitive to estrogens, through a mechanism that involves a well conserved ERE. This feature makes this gene an outstanding biomarker of xenostrogen exposure, and we have developed an in vivo assay allowing detection of estrogentic activity with a very high sensitivity. This assay is based on a transgenic zebrafish tg(cyp19a1b-GFP) line that expresses GFP in RGCs. By quantifying GFP expression in live fish, we show that short-term exposure of tg(cyp19a1b-GFP) embryos from 0 to 120 hpf to a variety of well established estrogenic compounds (estradiol, estriol, estrone, ethynylestradiol, zearalenone and its metabolites, nonyl, octyl and tert-pentylphenol, BPA, benzophenones derivates, etc.) turns on GFP expression in a concentration-dependent manner. Overall, we demonstrate the remarkable usefulness of the tgcyp19a1b-GFP) embryos as a reliable, sensitive and rapid in vivo estrogenic screening assay. This assay nicely complements the in vitro assay that we have previously developed using the same promoter coupled to luciferase. As we have also evidenced an effect of estrogens on the neurogenic activity of zebrafish, abnormal exposure of fish embryos to estrogenic endocrine disruptors is likely to affect the neurogenic process.

DOI: 10.1530/endoabs.32.S7.1

**S7.2**

Abstract unavailable.

DOI: 10.1530/endoabs.32.S7.2

**S7.3**

**Peptide hormones and receptors: why so many?**

Dan Larhammar

Uppsala University, Uppsala, Sweden.

Hormones and hormone receptors in mammals, including humans, display bewildering complexity. The evolution of peptide hormone families with multiple members has been difficult to resolve because of their short sequences. Their G-protein-coupled receptor families are challenging because they display variable sequence rates along the proteins, between species, and over time. My laboratory has therefore combined analyses of sequences with investigation of conserved synteny, i.e. comparisons of the chromosomal locations of the genes between species. This facilitates identification of true species homologs. Using these approaches we have been able to disentangle the evolutionary histories of endocrine peptide and receptor families. Invariably, we find that the ancestor of vertebrates must have had more gene family members than humans have today. This ancestral complexity is due to two gene doublings in early vertebrate evolution, leading to quadruplication of the ancestral chromosome set, thereby generating additional gene copies for many peptides and receptors. The NPY-PYY-pancreatic polypeptide family once had seven receptors, only four of which still exist in humans. Today humans have three vasopressin receptors, whereas the ancestral vertebrate had six. An ancient duplicate of prolactin is present in birds and fish, but was lost in the mammalian lineage. The somatostatin receptor family previously had six members, one of which was lost before the origin of mammals. One of the most extreme cases is the receptor family for the somatostatin-related peptide urotensin II: mammals have only a single receptor, but our ancestors possessed no less then five, all of which still exist in some vertebrates such as a lizard and a turtle. Thus, although our neuroendocrine system is certainly quite complex, we have clearly degenerated by gene loss. Furthermore, many fishes have gained additional gene copies by another genome doubling as well as local gene duplications. An important question arises: which functions have we and other mammals lost that still exist in other vertebrates?

DOI: 10.1530/endoabs.32.S7.3
Glucocorticoid action on the skeleton

Glucocorticoids (GCs) belong since their discovery to the standard therapy of rheumatoid arthritis (RA), a severe auto-inflammatory bone disease. One major side effect of GCs affects the skeleton itself leading to GC-induced osteoporosis (GIO), the most secondary osteoporosis.

To optimize anti-inflammatory therapies utilizing steroids a profound understanding of GC action on the interface of inflammation and skeletal integrity is required.

GCs act via a receptor (GR) that can alter gene expression by binding as a dimer to GR responsible elements in the promoter region of target genes or by interacting with and thus interfering with other transcription factors as a monomer. We determined the contribution of molecular mechanisms and cell types critically involved in anti-inflammatory effects of GCs in RA and on skeleton using conditional and function selective GR knockout mice.

We made the surprising observation that for suppression of inflammation in several arthritis models GR dimerization is absolutely required in part including a specific action in T cells.

In contrast for GC induced bone loss we demonstrated in a model of GIO that unexpectedly interaction of the GR monomer with AP-1, but not NF-kB in osteoblasts is decisive for bone loss.

Our findings define new criteria for SEGRM that act anti-inflammatory and protect the bone. Indeed we identified one lead-compound that still suppresses NF-kB dependent gene expression but does not affect osteoblast differentiation and activity.

Furthermore we identified novel GR target genes by functional genomics and developed a screening platform for novel GR agonist-derivatives not affecting osteoblast function.

Taken together, our approach gives new insights into GC action on arthritis and bone that can be translated into new concepts for anti-inflammatory therapies preventing GIO.

DOI: 10.1530/endoabs.32.S8.1

Osteoporosis: now and the future

Lorenz C Hofbauer
Dresden Technical University Medical Center and Center for Regenerative Therapies Dresden, Dresden, Germany.

Osteoporosis is an emerging medical and socioeconomic problem leading to fragility fractures, loss of mobility, chronic pain and cost to the individual and society. Diagnosis is often established only after fracture, although modern techniques exist to make the diagnosis early on where specific therapy is possible.

Apart from calcium and vitamin D supplementation and lifestyle counseling, bisphosphonates have become the mainstay of therapy. However, long-term effects are similar compared to short-acting GLP-1 receptor agonists, for once daily or once weekly injection have been developed in order to fully induce weight-loss in the majority of patients without an increased risk for hypoglycemia. Recently long-acting GLP-1 agonists with a prolonged half-life for once daily or once weekly injection have been developed in order to fully exploit the therapeutic potential of GLP-1 and improve clinical effects. Side effects are similar compared to short-acting GLP-1 receptor agonists, GI symptoms (nausea and vomiting) seem to occur less frequently. Much interest is focusing on the differentiation of molecules based on the half-life into long-acting versus short-acting GLP-1 receptor agonists, since it is increasingly apparent that exclusively short-acting molecules regulate glucose-metabolism.

DOI: 10.1530/endoabs.32.S8.3
also by inhibition of gastric emptying while long-acting molecules preferentially act by regulation of islet hormone levels. Thus, the perspective to combine GLP-1 based therapies with basal insulin may be an approach to effectively control both fasting and postprandial glycaemia. In long-standing type 2 diabetes basal insulin may be preferentially combined with short-acting GLP-1 receptor agonists, while in early stages of type 2 diabetes long-acting GLP-1 molecules may be used as well. These combination therapies also help to improve individualized diabetes treatment. In order to evaluate the effect of GLP-1 based therapies on clinical endpoints, the results of long-term intervention trials are eagerly awaited.

References

S9.2
Abstract for ESE Congress 2013
Early insulin treatment in type 2 diabetes
Peter M Nilsson
Department of Clinical Sciences, Skåne University Hospital, Lund University, 205 02 Malmö, Sweden.

The evidence base for starting early insulin treatment in patients with type 2 diabetes is rather scanty. In the UKPDS trial the intensive treatment of hyperglycaemia in newly detected patients with type 2 diabetes based on insulin or sulphonylurea (no separation possible) revealed a significant reduction of myocardial infarction risk (15%, P = 0.01), but only after prolonged post-study follow-up after 10 years. In 2012 the ORIGIN study was published showing no cardiovascular prevention in patients randomized to treatment with an insulin analogue (glargine) as compared to standard therapy. Taken together these two studies do not fully support early insulin treatment in patients with type 2 diabetes for cardiovascular protection. However, other clinical considerations might be of importance, and according to the most recent recommendations from EASD/ADA and their treatment algorithm there may be clinical indications also to support early insulin treatment in these patients not controlled by metformin alone. It should be remembered that some patients with type 2 diabetes in need of very early insulin treatment may instead have late autoimmune diabetes in the adult (LADA) when a diagnosis based on antibodies should be made.

S9.3
Ultra-long acting insulins
S Heller
University of Sheffield, Sheffield, UK.

The limitations of s.c. insulin lead to post prandial hyperglycaemia and a high risk of hypoglycaemia particularly in the post-absorptive state. Nocturnal hypoglycaemia continues to be a common and major problem for patients with insulin treated diabetes and is a major barrier in preventing patients reaching tight glycaemic targets. The development of basal insulin analogues, insulin glargine and insulin detemir which deliver insulin over a longer period more consistently and with less of a peak effect compared to human insulin are considered a useful advance. Meta-analyses have reported only modest benefit although importantly rates of nocturnal hypoglycaemia are rarely included as an end-point. Nocturnal hypoglycaemia is reduced usefully in many individuals and is a robust indication for the use of these insulins. In some individuals long-acting analogues can be administered once daily although many need two injections each day to provide full 24 h coverage. The development of ultra long acting insulin potentially offers a further advance with universal once a day administration and more stable background levels. Although a number of insulins of this type are being developed, only one has been brought to market. Insulin degludec (Tresiba) has been approved for use in Europe and Japan following an extensive clinical development programme. Clinical trials report encouraging and clinically relevant reduced rates of nocturnal hypoglycaemic episodes in patients with either type 1 diabetes or type 2 diabetes. In addition, the precise timing of administration is net critical and when given at varying time intervals still leads to stable background concentrations. A single injection of basal insulin in patients with type 1 diabetes brings new challenges in dealing with exercise and other lifestyle issues but ongoing work should provide guidance to clinicians and patients in adjusting insulin and calculating appropriate bolus doses.

S10.1
Salt-water balance

S10.2
Clinical aspects of diabetes insipidus and hyponatraemia
Gary Robertson
Northwestern University, Chicago, Illinois, USA.

Diabetes insipidus (DI) is a syndrome caused by various defects in the secretion or action of the anti-diuretic hormone, arginine vasopressin (AVP). They include impaired AVP production (pituitary DI), increased AVP degradation (gestational DI), suppression of AVP secretion by excessive water intake (primary polydipsia) or decreased antidiuretic effect due to various abnormalities in the kidney (nephrogenic DI). In all four types, the severity of the defect varies between patients. This complicates differential diagnosis by traditional methods based on the urinary response to fluid restriction and injection of AVP or its analogue, desmopressin. An alternative approach is now available. It begins with measurement of basal plasma AVP. If it is normal or elevated (> 2 pg/ml), the patient has nephrogenic DI and further testing can focus on the pathogenesis. If basal plasma vasopressin is low (<2 pg/ml), nephrogenic DI is excluded and a brain MRI to determine the absence or presence of the normal posterior pituitary ‘bright spot’ distinguishes pituitary DI from primary polydipsia. This method is more than 90% accurate as judged by the response to standard therapeutic doses of AVP or desmopressin. Hyponatraemia is also due to several different defects in the osmoregulation of antidiuresis. They include impaired suppression of AVP secretion due to non-osmotic stimuli (‘effective’ hyponatraemia, true hyponatraemia, nausea or cortisol deficiency) as well as inappropriate secretion of AVP (SIADH) due to ectopic production or primary defects in osmoregulation. The latter take various forms including down-regulation of AVP receptors. There is also an AVP-independent type of inappropriate antidiuresis caused by an activating mutation of the V2 receptor or other unidentified abnormalities. Differentiation between the various causes of hyponatraemia is a necessary part of the decision whether to treat with hypertonic saline, antiemetic, cortisol or an antagonist of the AVPR2 receptor.

S10.3
Antidiuretic: insights into the molecular regulation
Robert Fenton
Aarhus University, Aarhus, Denmark.

The water channel aquaporin-2 (AQP2) of the kidney connecting tubule and collecting ducts, plays an essential role in maintaining body water balance. AQP2 is regulated by the peptide hormone arginine vasopressin (AVP), which exerts parts of its effects through the type 2 vasopressin receptor (AVPPR2), expressed throughout the distal neuron. Disrupted function or regulation of AQP2 or the AVPPR2 results in nephrogenic diabetes insipidus (NDI). NDI is a common clinical condition of renal origin, which is most often characterized by polydipsia
and polyuria. Major research efforts have advanced our understanding of NDI at the genetic, cellular, molecular, and biological levels. In this talk I provide an overview of the cell biological causes of NDI. In addition, I provide an overview of some novel treatment strategies that have been recently proposed for alleviating the symptoms of some forms of NDI, such as those arising from lithium and other drug therapies, acute and chronic renal failure, and disturbed levels of calcium and potassium. I will also discuss cell biological mechanisms for bypassing G protein-coupled receptor signaling.

DOI: 10.1530/endoabs.32.S10.3

**New mechanisms in SST analogue response**

**$11.1$**

**Functional relevance of truncated SST5 receptor variants**

Raúl M Luque, Alejandro Ibáñez-Costa, Manuel D Gahte & Justo P Castaño

Department of Cell Biology, Physiology and Immunology, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), and CIBER Fisiopatología de la Obesidad y Nutrición, University of Córdoba, Córdoba, Spain.

Somatostatin (SST) and its related peptide cortistatin (CORT) exert multiple physiological actions through binding to a family of G-protein coupled receptors (sst1–sst5), commonly bearing seven transmembrane domains (TMDs). However, we have recently discovered that human, pig and rodent sst5 gene also generate, through non-canonical alternative splicing, novel truncated albeit functional sst5 variants that lack one or more TMDs. Our studies indicate that truncated sst5 variants are key elements of the sst family with unique molecular features and functional capacities in mammals, where they can directly interact with long, 7TMD variants (i.e. sst2) and modulate the normal and pathological cellular response to SST/CORT in terms of signaling pathways, hormone secretion and proliferation. Specifically, we have observed that human truncated sst5TMD4 is absent in normal pituitaries and mammary gland tissues but is present in pituitary and breast tumors, in association with long sst5 and/or sst2. In fact, our results indicate that sst5TMD4 might play a relevant patho-physiological role, probably by modulating/impairing the actions of long sst5, which are commonly used as pharmacological targets to treat endocrine/tumoral pathologies (octreotide/lanreotide). Indeed, when coexpressed in the same cell, truncated sst5TMD4 colocalizes and physically interacts with long sst5, providing a molecular basis for the ability of sst5TMD4 to disrupt the normal functioning of sst2/sst5. Moreover, our results indicate that sst5TMD4 is selectively expressed in certain types of tumours, which offer novel avenues to identify and develop original molecular targets for the future diagnosis, prognostic and/or therapeutic treatment of these human pathologies.

Declaration of funding


DOI: 10.1530/endoabs.32.S11.1

**$11.2$**

**Role of filamin A in dopamine and somatostatin receptor targeting in the pituitary**

Erika Peverelli

University of Milan, IRCCS Osp Maggiore Policlinico, Milan, Italy.

Molecular mechanisms underlying resistance of pituitary tumors to somatostatin (SS) and dopamine (DA) analogs treatment are not completely understood. Resistance has been associated with defective expression of functional SS (SSTR2–5) and DA (DRD2) receptors. The role of cytoskeleton proteins in receptor trafficking, anchoring to the plasma membrane and signalling has been demonstrated in other tumoral cell systems. In particular, filamin A (FLNA) seems to be a good candidate. In fact, it is implicated in the regulation of DRD2 localization and signalling in different cell types. In particular, we recently demonstrated that both FLNA and DRD2 are strongly reduced or absent in DA-resistant prolactinomas. Moreover, FLNA overexpression in primary cultured cells from resistant prolactinomas restores D2R expression and PRL responsiveness to DA. On the contrary, in cultured cells from DA-sensitive prolactinomas and MMQ cells FLNA silencing resulted in a reduction of D2R expression and abrogation of DA-induced inhibition of PRL release and antiproliferative signals. These data indicate that FLNA is crucial for D2R expression and signaling in lactotrophs, suggesting that the impaired response to DA may be related to the reduction of FLNA expression in DA-resistant prolactinomas.

Since SSTR2 was recently found to associate with FLNA, we investigated a possible role of FLNA in regulating SSTR2 targeting and signalling in GH-secreting adenomas. To this purpose, we performed FLNA silencing in GH-secreting adenoma cultured cells. Preliminary data showed that FLNA silencing did not affect neither SSTR2 localization at the plasma membrane nor its expression stability. On the contrary, the reduction in cyclin D1 levels induced by the selective SSTR2 agonist was abolished in FLNA silenced cells, suggesting that FLNA might be implicated in intracellular signalling of SSTR2 by mediating its antiproliferative effects without affecting receptor expression and localization at the plasma membrane.

DOI: 10.1530/endoabs.32.S11.2

**$11.3$**

**Role of ERK in somatostatin receptor signalling**

Anne Barlier1,2, David Romano2,3, Caroline Zeiller2, Cathy Roche2,3, Morgane Pertuit2,3 & Corinne Gerard1,2

1Aix-Marseille University, Marseille, France; 2CRN2-M-UMR 7286 CNRS, Marseille, France; 3AP-HM- La Conception, Marseille, France; 4Systems Biology Ireland-Conway Institute, Dublin, Ireland.

The Ras/Raf/MEK/ERK is a conserved signalling pathway involved in the control of fundamental cellular processes. Despite extensive research, how this pathway can process a myriad of diverse extracellular inputs into specific biological outcomes is not fully understood. Particularly, the role of this pathway in neuroendocrine tumoral cells remains unclear.

We have previously shown that the ERK1/2 pathway is an integrative point in the control of the pituitary function exerted by various extracellular signals. Moreover we established that the cross talk between the cAMP pathway and the ERK cascade is crucial for the fine regulation of hormonal transcription. In somatotroph tumoral cells, we have shown that the gsp-oncogene (due to an activating mutation of Gx) induced a sustained activity of ERK1/2 that is involved in the hormonal promoter activation through the GTPases Ras and Rap1.

Recently, using the FRET-based biosensors of ERK activity (EKAR), we established that both the EGFR receptor and the GPCR coupled to the CAMP-pathway tightly control the spatiotemporal dynamic of activated ERK with different magnitude and duration through the specific recruitment of Ras and Rap1. Moreover, in human pituitary tumors, Dworakowska et al. showed that raf/MEK/ERK pathway is up-regulated. It is well known that octreotide exerts an inhibitory effect on hormonal secretion of pituitary and neuroendocrine cells through the CAMP pathway. A slight but significant inhibitory effect was also observed on tumoral growth and cell proliferation but the signalling mechanisms underlying such an antiproliferative effect remains unclear. Using a somato-lactotroph cell line expressing the sst2 receptor, we identified an opposite effect of ligand-independent and octreotide-dependent sst2 activity on the ERK1/2 activity. The molecular mechanisms involved in SST2-dependent ERK activity is currently under investigation.

DOI: 10.1530/endoabs.32.S11.3

**Male reproductive endocrinology**

**$12.1$**

**Semaphorin 3A: a new gene involved in Kallmann syndrome**

Jacques Young

Endocrinology and Reproductive Diseases Department, Hôpital Bichat, Université Paris Sud et Assistance Publique Hôpitaux de Paris, Paris, France.

Kallmann syndrome (KS) is a genetic disorder associating pubertal failure with congenital absent or impaired sense of smell. KS is related to defective neuronal development affecting both the migration of olfactory nerve endings and GnRH neurons. The discovery of several genetic mutations responsible for KS led to the identification of signaling pathways involved in these processes, but the mutations so far identified account for only 30–40% of cases of KS. We attempted to identify new KS responsible genes by using a pangenomic approach and we identified SEMA3A. Thus, from an initial cohort of 120 KS patients, we first
studied 48 propositi with no mutations in known KS genes. They were analyzed by CGHarray, using Agilent 105K oligonucleotide chips with a mean resolution of 50 kb. We first found one propositus who had a heterozygous deletion of 213 kb at locus 7q21.11, confirmed by real-time qPCR, deleting 11 of the 17 SEMA3A exons. This deletion co-segregated in the propositus’ family with the KS phenotype. Later, thanks to a French and European network, additional non-synonymous heterozygous mutations in 24 patients, a frameshifting small deletion (538fsX31) and seven different missense loss of function mutations were reported. SEMA3A codes for semaphorin 3A, a protein that interacts with neuropilins. Interestingly, mice lacking semapharin 3A expression have been showed to have a Kallmann-like phenotype. SEMA3A is therefore a new gene with a loss of function is involved in KS. These findings validate the specific contribution of semaphorin 3A to the development of the olfactory system and in neuronal control of puberty in humans. The mode of inheritance (autosomal dominant or recessive or oligogenic) of this novel genetic form remains to be clearly established in familial and sporadic KS cases. Reproductive phenotypes and gonadotropin axis abnormalities in SEMA3A mutated KS patients and specifically the absence of associated neurological or non neurological clinical disorders will be discussed.

Hormonal treatment in transition of patients with rare diseases

S13.1
Hormonal treatment in transition of patients with Prader–Willi syndrome
Charlotte Höybye
Karolinska University Hospital, Stockholm, Sweden.

Introduction
Prader–Willi syndrome (PWS) is a complex genetic disorder caused by the absence of normal activity in the paternally expressed genes from the chromosome 15q11–q13. PWS is typically characterised by hyperphagia, muscular hypotonia, developmental and cognitive delay, behavioural problems and endocrine abnormalities. Obesity and short stature are common. Controlled studies of hormonal treatment in the transition period are not available.
Endocrine insufficiencies
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 insufficiency. GH treatment initiated during childhood normalises skeletal growth, improve body composition and optimize 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 performance. 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 IGF1 and sleep related breathing disorders. Incomplete sexual development is frequently seen in PWS. The majority has clinical and laboratory measurements demonstrating hypogonadism, and 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 recently been hypothesized to be responsible of 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 when clinically indicated. Hypothyroidism is not common in PWS, but TSH and thyroid hormones should be monitored and treated.

Central adrenal insufficiency has recently been hypothesized to be responsible of 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 when clinically indicated. Hypothyroidism is not common in PWS, but TSH and thyroid hormones should be followed regularly.

Conclusion
PWS is associated with documented endocrine insufficiencies which should be monitored and treated.

S13.2
Transition of females with Turner syndrome
Claus H Gravholt
Department of Endocrinology and Internal Medicine, Aarhus University Hospital, 8000 Aarhus C, Denmark.

Treatment with GH during childhood and adolescence allows a considerable gain in adult height. SHOX deficiency explains some of the phenotypic characteristics in TS, principally short stature. Puberty has to be induced in most cases, and female sex hormone replacement therapy should continue during adult years. These issues are normally dealt with by the paediatrician, but once a TS female enters adulthood it is less clear who should be the primary care giver. Morbidity and mortality is increased, especially due to the risk of dissection of the aorta and other cardiovascular diseases, as well as the risk of type 2 diabetes, hypertension, osteoporosis, thyroid disease and other diseases. The proper dose of hormone replacement therapy (HRT) with female sex steroids

S12.2
Signal transduction in sperm functions
Zvi Naor
Department of Biochemistry and Molecular Biology, George S. Wise Faculty of Life Sciences, Tel Aviv University, Ramat Aviv 69978, Israel.

Mature spermatozoa acquire progressive motility only after ejaculation. Their journey in the female reproductive tract also includes suppression of progressive motility, reactivation, capacitation, and hyper-activation of motility (whiplash), the mechanisms of which are obscure. MAPKs are key regulatory enzymes in cell signaling, participating in diverse cellular functions such as growth, differentiation, stress, and apoptosis. We have reported that ERK1/2 and p38MAPK are primarily localized to the tail of mature human spermatozoa. Surprisingly, c-Jun N-terminal kinase 1/2 (JNK), which is thought to be ubiquitously expressed, could not be detected in mature human spermatozoa. ERK1/2 stimulation is downstream to protein kinase C (PKC) activation, which is also present in the human sperm tail. ERK1/2 stimulates and p38 inhibits forward and hyper-activated motility, respectively. Hence, a rise in ERK1/2 will induce progressive motility, while a rise in p38 may induce suppression of progressive motility. Concomitant increase in both ERK1/2 and p38 may induce hyperactivation of motility. Both ERK1/2 and p38 MAPK are involved in the acrosome reaction. Using a proteomic approach, we identified ARHGAP6, a RhoGAP, as an ERK substrate in PMA-stimulated human spermatozoa. Inverse correlation was obtained between the relative expression level of ERK1 or the relative activation level of p38 and sperm motility, forward progression motility, sperm morphology, and viability. Therefore, increased expression of ERK1 and activated p38 can predict poor human sperm quality.

S12.3
Small RNAs in spermatogenesis
Noora Kotaja
University of Turku, Turku, Finland.

The protection of genetic integrity and establishment and maintenance of correct epigenetic marks are crucial in the germ line to prevent transmission of harmful information to next generations. Male germ cell differentiation is governed by accurate, spatially and temporally controlled gene expression patterns. Male germ cells produce several classes of small non-coding RNAs that are known to regulate gene expression at both post-transcriptional and transcriptional level. These include Dicer-dependent microRNAs (miRNAs) and endogenous small interfering RNAs (endo-siRNAs), and Dicer-independent piwi-interacting RNAs (piRNAs). The functions of these small RNAs in male germ cell-specific gene regulation are still largely unclear. The goal of our research is to clarify the roles of small non-coding RNAs and the mechanisms of post-transcriptional gene control during male germ cell differentiation. We have shown that Dicer is required for spermatogenesis by using a knockout mouse model with Dicer1 gene deletions. piRNAs accumulate in an intriguing cytoplasmic granule, a chromatoid body (CB). We have isolated CBs from mouse testis and characterized its molecular composition to better understand the role of the CB in the post-transcriptional RNA regulation in haploid cells. These pathways appear to be essential for normal spermatogenesis in mouse, thus highlighting their significance in maintaining male fertility.

Hormonal treatment in transition of patients with Prader–Willi syndrome
Charlotte Höybye
Karolinska University Hospital, Stockholm, Sweden.

Introduction
Prader–Willi syndrome (PWS) is a complex genetic disorder caused by the absence of normal activity in the paternally expressed genes from the chromosome 15q11–q13. PWS is typically characterised by hyperphagia, muscular hypotonia, developmental and cognitive delay, behavioural problems and endocrine abnormalities. Obesity and short stature are common. Controlled studies of hormonal treatment in the transition period are not available.
Endocrine insufficiencies
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 insufficiency. GH treatment initiated during childhood normalises skeletal growth, improve body composition and optimize 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 performance. 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 IGF1 and sleep related breathing disorders. Incomplete sexual development is frequently seen in PWS. The majority has clinical and laboratory measurements demonstrating hypogonadism, and 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 recently been hypothesized to be responsible of 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 when clinically indicated. Hypothyroidism is not common in PWS, but TSH and thyroid hormones should be followed regularly.
Conclusion
PWS is associated with documented endocrine insufficiencies which should be monitored and treated.

S13.2
Transition of females with Turner syndrome
Claus H Gravholt
Department of Endocrinology and Internal Medicine, Aarhus University Hospital, 8000 Aarhus C, Denmark.

Treatment with GH during childhood and adolescence allows a considerable gain in adult height. SHOX deficiency explains some of the phenotypic characteristics in TS, principally short stature. Puberty has to be induced in most cases, and female sex hormone replacement therapy should continue during adult years. These issues are normally dealt with by the paediatrician, but once a TS female enters adulthood it is less clear who should be the primary care giver. Morbidity and mortality is increased, especially due to the risk of dissection of the aorta and other cardiovascular diseases, as well as the risk of type 2 diabetes, hypertension, osteoporosis, thyroid disease and other diseases. The proper dose of hormone replacement therapy (HRT) with female sex steroids
Endocrine Abstracts (2013) Vol 32

S13.3 Hormonal treatment of patients with Klinefelter syndrome during transition
Jean de Schepper
UZ Brussel, Brussels, Belgium.

Hormonal management of androgen, secondary thyroid hormone and vitamin D insufficiency of patients with Klinefelter syndrome (KS) during transition needs some expertise. While vitamin D supplementation should be smoothly applied, thyroxin should be reserved for primary (auto-immune) thyroid disease. Although the androgen deficiency is generally mild and slowly progressive, timely initiation of testosterone replacement therapy (TRT) has been advocated to ensure a normal adult sexual development and to prevent the consequences of long-term androgen deficiency. However, it is unclear if typical complaints and signs of KS, such as decreased facial and body hair, emotional and social developmental delay, eunuchoid body proportions and poor muscle development are fully corrected by TRT. In addition, the efficacy of TRT in the prevention of the metabolic syndrome, varicose veins, leg ulcers, breast cancer and auto-immune diseases is not clearly defined. On the other hand, careful dose adjustment of testosterone is needed to avoid chronic overexposure, given the higher risk of prostate cancer and aggressive behaviour. Cryopreservation of semen samples or testicular tissue should be considered before initiating TRT. It is unknown whether the suppressive effect of TRT on spermatogenic function is fully reversible and is dose and route of application dependent. On the other hand, testosterone has beneficial effects on semen volume and prostate volume.

Additional therapy with aromatase inhibitors can be considered in patients with gynecomastia, obesity or elevated E2 concentrations or prior to sperm retrieval. Changing dose or route of application of TRT is frequently considered in vain to relieve inherent KS specific physical and psychological problems as chronic fatigue, low vitality, decreased concentration and mood changes. Compliance with daily gel administration is challenging for transition patients. Frequent patient visits may be necessary to maintain and assess compliance, to discuss safety and preventive measures and to avoid discouragement.

DOI: 10.1530/endoabs.32.S13.3

S14.1 Clinical care of the pheochromocytoma patient
Henri Timmers
Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.

Paragangliomas (PGLs) derive from either sympathetic tissue in adrenal and extra-adrenal locations, or from parasympathetic tissue of the head and neck. Adrenal PGLs are usually referred to as pheochromocytomas. Most patients with adrenal and extra-adrenal abdominal PGLs have increased plasma and urine concentrations of catecholamines (dopamine, norepinephrine and epinephrine). Typical symptoms and signs of catecholamine excess include headache, palpitations, diaphoresis, and hypertension. Although PGL is a rare cause of hypertension, the diagnosis is considered frequently by clinicians in patients with refractory hypertension or symptoms or signs of catecholamine excess. In about 8-9% of patients with sporadic PGL and 21-31% with hereditary PGL, plasma concentrations and urinary outputs of catecholamines are normal. Nevertheless, such patients invariably have elevated plasma concentrations of the metanephrines, normetanephrine and metanephrine. These O-methylated metabolites of norepinephrine and epinephrine are produced continuously within tumor cells and independently of catecholamine release, which can be variable or negligible, even in patients with large tumors. Exceptions where plasma metanephrines can be normal include patients with very small tumors (<1 cm) that do not synthesize and metabolize sufficient amounts of catecholamines to produce positive test results. Other rare exceptions include patients with PGLs that only produce dopamine and which may be detected by increases in plasma methoxytyramine, the O-methylated metabolite of dopamine. In contrast to PGLs derived from sympathetic tissue, the vast majority (95%) of head and neck PGLs do not produce significant amounts of (nor)epinephrine.

At least 30% of the PGLs are caused by germline mutations in ten identified tumor susceptibility genes viz., RET, NF1, VHL, succinate dehydrogenase subunits A, B, C, D and assembly factor 2 (SDHADC/B/C/D/A/F-2), TMEM127 and MAX. These genotypes correlate with distinct biochemical phenotypes characterized by differences in catecholamine metabolobal and secretory signatures.

DOI: 10.1530/endoabs.32.S14.1
Finally, future trends in functional imaging, including its use in pharmacodynamics and molecular imaging, tightly linked to individualized medicine to ‘secure’ the optimal therapeutic plan, will also be outlined.

DOI: 10.1530/endoabs.32.S14.2

S14.3
Treatment of malignant pheochromocytomas and paragangliomas
E Baudin
France.

Pheochromocytomas and paragangliomas are rare neuroendocrine chromaffin tumors located in the adrenal or extra-adrenal sites, respectively. Malignant pheochromocytomas or paragangliomas represent 10–20% (MPP) of these patients and are defined by the presence or occurrence of metastasis, in non chromaffin organs. MPP are characterized by their heterogeneous presentation as testified by their variety in primary locations, levels and type of hormone secretions, percentage of genetic disorders and finally frequency of bone metastatic locations. Due to their scarcity, prognostic of MPP have been seldom studied but a hudge heterogeneity in survival has been suggested. SDHB mutation but also the primary location or hormone secretions may constitute critical prognostic parameters. Treatment of MPP has two main goals: the control of hormone-related symptoms and tumor-related burden. In the absence of curative options for advanced MPP patients and randomized trials, the balance between benefits of therapeutic interventions and their safety should be carefully weighed, within skill expert centers and networks, especially in asymptomatic MPP patients with slow rate of progression and low tumor burden. Multiple locoregional options are available to control local progression but also systemic therapies that include meta-iodo-benzyl-guainidine (MIBG) or peptide receptor radionucule therapy but also, dacarbanzole-based-chemotherapy regimen. Recently antiangiogenic therapy has been reported to provide benefit in MPP patients. Protocols are now available for MPP patients, like the first randomized trial in malignant progressive pheochromocytomas or paragangliomas (FIRS-MAPP) trials in Europe, and can be considered as a first line option in progressive MPP.

DOI: 10.1530/endoabs.32.S14.3

The Frail Male
S15.1
Sarcopenia in men: the endocrine perspective
Manthos Giannoulis
Private Practice, Thessaloniki, Greece.

The improvement of physical function and mobility in a continuously expanding elderly population emerges as high priority of medicine today. Muscle mass, strength and maximal exercise capacity are major determinant of physical function and all have been shown to decline with aging which may contribute to the increase incidence of frailty and disability observed in elderly men whereas the decline in exercise capacity may facilitate the accumulation of body fat and insulin resistance.

Muscle adaption to exercise seems to be modulated by anabolic circulating endocrine hormones and by autocrine/paracrine local growth factors, which are all load sensitive. GH, IGF1 and T are directly involved in muscle adaptation to exercise as promote muscle protein synthesis whereas T and a locally expressed IGF1 has been reported to activate muscle stem cells called satellite cells. While exercise improves physical function, elderly men fail to sustain an exercise program and a suitable program has yet to be established. GH/IGF1 axis function and T levels decline markedly with aging, which indeed may explain the blunted response of muscle adaptation to exercise observed in elderly men.

Several studies have reported that administration of T improves muscle function in health elderly men. Conversely, GH failed to improve physical function despite the amelioration of detrimental somatic changes of aging. There are evidence of synergistic anabolic action of GH and T and few studies that used this approach have reported greater efficacy. Future studies would need to assess the clinical applicability of these findings as gathering evidence support the indispensable role of endocrine function on physical function integrity.

DOI: 10.1530/endoabs.32.S15.1

S15.2
Male osteoporosis
Richard Eastell
University of Sheffield, Sheffield, South Yorks, UK.

Osteoporosis is a silent disorder characterized by reduced bone strength predisposing to increased fracture risk. Although osteoporosis affects women more often than men, ~20% of the 44 million Americans who have osteoporosis or low BMD are men. Between 30 and 40% of fractures due to osteoporosis occur in men; the lifetime risk of fracture for men aged 50 or older is between 13 and 30%. Osteoporosis in men causes significant morbidity and mortality. The major mechanism underlying bone loss with ageing in men is sex hormone deficiency, both testosterone and oestradiol. Men’s larger bones are likely a consequence of testosterone’s effect on periosteal apposition and this contributes to greater bone strength. There are other reasons why men have fewer fractures than women. Men fall less often than women; higher androgen levels have been associated with reduced fall risk. Finally, men have a shorter life expectancy. The European Society for Endocrinology worked with the Endocrine Society to develop guidelines for male osteoporosis1. They recommended testing higher risk men (aged ≥70 and men aged 50-69 who have risk factors (e.g. low body weight, prior fracture as an adult, smoking, etc.)) using central dual-energy X-ray absorptiometry. Laboratory testing should be done to detect contributing causes. Adequate calcium and vitamin D and weight-bearing exercise should be encouraged; smoking and excessive alcohol should be avoided. Pharmacological treatment is recommended for men aged 50 or older who have had spine or hip fractures, those with T-scores of −2.5 or below, and men at high risk of fracture based on low bone mineral density and/or clinical risk factors. Treatment should be monitored with serial dual-energy X-ray absorptiometry testing.

Reference

DOI: 10.1530/endoabs.32.S15.2

S15.3
Cognitive decline in male ageing
John Starr
University of Edinburgh, Edinburgh, Scotland, UK.

Introduction
This is a review of cognitive decline in male ageing.

Methods
Literature review and analysis of cognitive data from the Healthy Old People of Edinburgh (born 1905–1919), Lothian Birth Cohort 1921 and Lothian Birth Cohort 1936 studies.

Results
Cognitive scores in men increased relative to those of women between childhood and late adulthood, but changes in old age were little affected by sex once other factors, such as education, were adjusted for.

Conclusions
Male cognitive ageing differs from women’s in early and mid-adulthood, but these differences mostly disappear later in life.

DOI: 10.1530/endoabs.32.S15.3
Oncogenic signals in thyroid cancer - therapeutic prospects S16.1

BRAFV600E and PIK3CAH1047R cooperate to promote progression of anaplastic thyroid carcinoma in the mouse
Roch-Philippe Charles1,2, Jilian Silva1,2, Gioia Iezza3, Wayne A Philips4 & Martin McMahon1,2
1Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, California, USA; 2Department of Cell and Molecular Pharmacology, University of California, San Francisco, California, USA; 3Department of Pathology, University of California, San Francisco, California, USA; 4Surgical Oncology Laboratory, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia.

Thyroid malignancies are the most common type of endocrine tumors. Of the various histological sub-types, anaplastic thyroid carcinoma (ATC) represents 2% of all cases but is responsible for most of the thyroid cancer related death. Indeed, ATC is regarded as one of the more aggressive and hard to treat forms of human cancer. Moreover, to date, there is a paucity of relevant models to study how the signature genetic abnormalities detected in ATC contribute to the pathogenesis of this disease. Mutational activation of the BRAF proto-oncogene is detected in ~40% of papillary thyroid cancers (PTC) and also in a significant percentage of ATC. Moreover, BRAF mutation is frequently found in combination with gain-of-function mutations in PIK3CA (encoding the p110 catalytic subunit of PI3'-kinase-a) or loss-of-function alterations in either TP53 or PTEN. Using mice with conditional, thyrocyte-specific expression of BRAFV600E, we have previously described a model of PTC1. However, as in humans, BRAFV600E-induced PTC in mice is indolent and rarely leads to lethal disease. Using mice carrying a conditional allele of Pik3ca (lat-1047R)2 we demonstrate that expression of mutational activated PIK3CAH1047R is largely without effect in thyrocytes. However, when BRAFV600E is expressed with PIK3CAH1047R in thyrocytes, mice develop ATC that results in rapid lethality. These data indicate that BRAFV600E cooperates with PIK3CAH1047R to promote progression of ATC in the mouse. This genetically relevant mouse model of ATC will be an invaluable platform for testing pathway-targeted therapies for the prevention and treatment of thyroid cancer in the preclinical context.

References

DOI: 10.1530/endoabs.32.S16.1

S16.2

Abstract unavailable.

DOI: 10.1530/endoabs.32.S16.2

S16.3

Oncogenic activation in thyroid cancer and response to radioiodine
J Ricarte-Filho
University of Sao Paulo, Sao Paulo, Brazil.

Metastatic thyroid cancer that are radioactive iodine-refractory (RAIR) have a high mortality, particularly if positive on [(18F)fluorodeoxyglucose (FDG)]-positron emission tomography (PET). We now have a better understanding of the genetic alterations implicated in the disease. Several studies along the last years have shown that constitutive activation of the mitogen-activated protein kinase (MAPK), triggered by rearrangements of RET and NTRK1 and activating mutations of RAS and BRAF, has a causal role in these formation of thyroid tumors. We have recently shown that RAIR, FDG-PET-positive metastases are specially enriched for BRAF mutations. Moreover, when BRAF or RAS are mutated in the primary tumor, it is likely that the metastases will harbor the same alteration. Also, we found that metastatic lesions have alterations in genes of the phosphoinositide 3-kinase (PI3K) pathway such as PIK3CA and AKT1, commonly in concomitance with MAPK activation. In contrast to BRAF alterations, PIK3CA/AKT1 mutations status in different specimens from the same patient are frequently divergent because these mutations arise during progression. These findings are important when considering targeted therapies for metastatic tumors. In fact, the use of the MAPK kinase (MEK) 1 and MEK2 inhibitor selumetinib (AZD6244, ARRY-142886) in patients with metastatic thyroid cancer showed that the drug increases iodine uptake and retention, particularly in RAS-mutant patients. Despite the recent advances and increasing knowledge acquired during the last years, a fraction of these aggressive tumors has no identified driver alterations. The use of the most recent sequencing technologies is helping to uncover the additional genetic changes harbored by these patients.

DOI: 10.1530/endoabs.32.S16.3

Medical treatment of endocrine malignancies - an update S17.1

Pituitary carcinoma
Ashley Grossman
University of Oxford, Oxford, UK.

Pituitary tumours have recently been shown to have a prevalence of around one in a 1000, but the overwhelming majority of these are benign and readily treated. Nevertheless, while the initial therapy of the majority of non-secreting macroadenomas is transphenoidal surgery, these have a high tendency to recur; recurrence cannot at present be predicted by any histopathological markers. Indeed, some 50% of such adenomas will recur over 10 years, although this recurrence rate is reduced to <5% with standard external beam radiotherapy. Such radiotherapy, while highly effective, does carry the risk of progressive hypopituitarism, but the risk of second tumour development or of visual path abnormalities is very low. Only around 0.2% of pituitary tumours are carcinomas, as defined by the presence of intra- or extra-cranial metastases, but these offer an exceptional challenge. The majority of these tumours are either prolactin- or ACTH-secreting tumours, and it is interesting that non-functioning and somatotroph adenomas show evidence of ‘senescence’ markers, which are absent in ACTH- and prolactin-secreting adenomas. Patients with carcinomas may occasionally respond to dopamine- or somatostatin-receptor agonists, but in general require repeated transphenoidal or even transcranial surgery. Conventional chemotherapy is generally ineffective, but recent reports with the alkylating agent temozolomide have shown cases of impressive tumour control, at least in the short term. The enzyme MGMT reverses the effect of temozolomide by removing the methyl adduct from DNA, and reports suggest that tumours lacking MGMT are especially sensitive to temozolomide. However, an extensive study has shown that only some 15% of pituitary adenomas lack MGMT, and it is probably reasonable to consider temozolomide therapy for 3–6 months regardless of MGMT status, which is in any case difficult to quantify. In theory, tumours which remain progressive following temozolomide may respond to everolimus, an mTOR inhibitor, but data on this are scanty.

DOI: 10.1530/endoabs.32.S17.1

S17.2

Medical treatment of adrenocortical cancer
Jérôme Bertherat1,2
1Referral Center for rare adrenal diseases, Cochin Hospital, Paris, France; 2INSERM U1016, Paris, France.

Adrenocortical cancer (ACC) is a rare tumor with an overall poor prognosis. However outcome is heterogeneous and the indication and type of medical therapy should be personalized on the basis of tumor stage and prognostication. The initial diagnostic and extension work-up of an ACC is an important step. Most patients with ENSAT stage 1–3 ACC and some stage 4 ACC will be operated and pathological analysis is important for management. The goals of medical treatment are to control steroid excess and tumor development. Symptomatic treatment and steroidogenesis inhibitors can be used to control the consequences of secreting ACC. Mitotane is usually the drug of choice for both its anticortisolic and adrenolytic effects. However, due to its long delay of action it can be associated in severe cortisol secreting ACC with other drugs like metyrapone and/or ketoconazole, which have a faster effect. Mitotane can also be discussed as adjuvant therapy after complete removal of a tumor for its adrenolytic effect to prevent tumor recurrence. Retrospectives studies have shown a longer disease free survival with adjuvant mitotane, but this has not be a constant finding. One should keep in mind that the probability of recurrence varies among stage 1 and 2 ACC and that development of pathological or molecular

Endocrine Abstracts (2013) Vol 32
markers for risk assessment will help. In case of tumor recurrence or in metastasized ACC, medical therapy with mitotane is used and adapted to its plasma levels. Cytotoxic chemotherapy will be discussed depending on the rate of tumor progression and the response to mitotane. The FIRM-ACT trial has shown, in patients treated with mitotane, a better response rate and progression free survival using etoposide-doxorubicine-cisplatin than streptozotocine. Others cytotoxic chemotherapies and targeted therapies have been used in progressive ACC with lower response rate and will be summarized. Since most ACC overexpress GF2 the IGFs inhibitors have been developed. International efforts in prospective therapeutic trials are developed in this field. For this goal patient management in coordination with expert centers and networks of clinical research (in Europe www.endo.org) are important.

DOI: 10.1530/endoabs.32.S17.2

PCOS

S18.1

Environmental impact on the PCOS phenotype
Gerard Conway
University College London, London, UK.

The action of insulin acting as a co-gonadotrophin in women with PCOS has long been a focus of research. In western populations, a key environmental effect on PCOS is through the obesity epidemic. The resulting insulin resistance has direct effects on the clinical manifestation of PCOS with serum insulin showing positive associations with BMI, serum testosterone, AMH and variably with ovarian volume. AMH is a particularly interesting marker of PCOS with respect to insulin as diverse results have been found with BMI where associations have been found to be either negative or non-existent.

The characteristics of South Asian women with PCOS has been a point of interest over recent years because of the propensity to insulin resistance and type 2 diabetes in this population. While the prevalence of metabolic syndrome has been well documented, relatively little is known about the ovarian response to insulin status in women with PCOS in this region. South Asian women with PCOS have relatively mean low BMI and it is possible to explore the effects of insulin resistance at a lower end of the spectrum than is possible in many western cohorts.

The nature of development in much of India provides an interesting model to explore the effects of environment on PCOS. In rural areas women take a simple diet of millet and undertake physical labour in agriculture. There is then a period of diet and activity through to an urbanised group who have a considerable intake of refined carbohydrate and ‘junk food’ and who take little exercise. Preliminary data from India shows a major impact from lifestyle on several ovarian markers in PCOS including serum AMH concentrations.

DOI: 10.1530/endoabs.32.S18.1

S18.2

PCOS in adolescence: towards a therapy targeting adipose tissue
Lourdes Ibáñez
University of Barcelona, Esplugues, Barcelona, Spain.

PCOS is a common endocrinopathy in women that has traditionally been viewed as an ovarian disorder. Accordingly, the classic therapeutic approach, even in adolescents without pregnancy risk, is to silence the ovaries with an oral contraceptive (OC). Recent evidence indicates that PCOS is primarily a disorder of adipose-tissue hyperexpansion that may originate in early life, develop across childhood and puberty, and reach a full-blown stage in adolescence, manifesting with ovulatory dysfunction and symptoms of androgen excess. This novel concept implies that intervention should rather aim at reducing adipose-tissue hyperexpansion, and thus at correcting the associated insulin resistance, visceral adiposity and low-grade inflammation.

In non-obese PCOS adolescents without pregnancy risk, a low-dose combination of flutamide (Flu, an androgen-receptor blocker) and metformin (Met, an insulin-sensitizer) proved superior to a drosipirenone-OC in correcting the endocrine- metabolic and body-composition anomalies. In young PCOS women receiving OCs, the addition of low-dose pioglitazone (Pio), to the FluMet combination further increased lean body mass and HMW-adiponectin, and further reduced carotid intima-media thickness (cIMT).

Recently, we compared the effects of low-dose PioFluMet to those of an OC containing ethinylestradiol-cypionate (EE-CA). Both treatments reduced androgen excess similarly, but had divergent effects on glucose-induced insulinemia, visceral adiposity, low-grade inflammation, cIMT, menstrual regularity and on the expression in subcutaneous fat of genes related to macrophage activation, fat accretion, inflammation, and lipoprotein metabolism. These divergences were to the advantage of PioFluMet, and were still evident 6 mo post-treatment.

In conclusion, the intervention for reducing androgen excess in adolescence influences the post-treatment phenotype, as judged by markers of insulin sensitivity, visceral adiposity, arterial health, low-grade inflammation and menstrual regularity. A novel low-dose combination of insulin sensitizers plus an anti-androgen holds potential as a pathophysiologically-based treatment of PCOS in adolescence and prevents part of the androgen-excess phenotype in adulthood, including adiposity and subfertility.

DOI: 10.1530/endoabs.32.S18.2

S18.3

The diagnosis of PCOS in adults: new biomarkers
Renato Pasquali
University of Bologna, Alma Mater Studiorum, Bologna, Italy.

The National Institute of Health (US) recently organized an Evidence-based Methodology Workshop on the polycystic ovary syndrome (PCOS), focused on definition of the syndrome. Among others, the conclusions included the following: i) the need to assign a name that reflects the complex interactions that characterize the syndrome; ii) it is advisable to maintain a broad, inclusionary diagnostic criteria of Rotterdam, while specifically identifying the most common phenotype, characterized by androgen excess and ovulatory dysfunction; iii) the need to improve the methods and criteria used to assess androgen excess and develop an accurate assay for androgen levels; iv) it is necessary to improve the methods and criteria used to assess ovulatory dysfunction; v) it is necessary to investigate whether specific phenotypes of PCOS are associated with increased CV and diabetic complications. These recommendations intrinsically imply the need for further biomarkers. Potential biomarkers of ovarian dysfunction might be the measurement of blood levels of anti-Mullerian hormone and insulin like factor 3. The use of LM-MS/MS provides an important improvement in the assay of androgens. The combination of an extremely useful clinical parameter, ancahthosis nigricans, combined with adiponectin and insulin blood levels may help in defining the presence of insulin resistance. Low sex hormone-binding globulin may be a marker of insulin and androgen excess and might predict the susceptibility to develop type 2 diabetes. Finally, consistent with the available literature on the role of low-grade inflammation in the pathophysiology of androgen excess and metabolic disturbances, measuring specific markers such as TNF-a may help in characterizing specific phenotypes.

DOI: 10.1530/endoabs.32.S18.3

Recent advances in the molecular study of endocrine tumours: microRNAs and more

S19.1

TGF-β signaling and the microRNA machinery
Attila Patocs
Molecular Medicine Research Group, Hungarian Academy of Sciences and Semmelweis University, Budapest, Hungary.

The activin/transforming growth factor-β (TGF-β) is a family of evolutionary conserved polypeptides. Their role has been implicated in the regulation of embryonic development, reproduction and tumor formation. Related to tumorigenesis TGF-β signaling inhibits cell proliferation at multiple levels by i) inducing the expression of tumor suppressors p15Ink4b and p21Cip1, ii) repressing oncogenic factors such as c-MYC and Id proteins, iii) by activation apoptosis and iv) inhibiting tumor growth by repressing hepatocyte growth factor (HGF), macrophage-stimulating protein (MSP) and TGF-α. Loss of members of
the TGF-β signaling by somatic mutations or epigenetic events, such as DNA methylation or regulation by microRNA (miRNA) have been demonstrated to affect the signaling process. MiRNAs are 19-25 nucleotides long, non-coding RNA molecules that posttranscriptionally regulate gene expression via RNA interference. At least 30–50% of all protein-coding genes are under regulation of miRNAs. Their expression is highly tissue-specific, and one miRNA affects the expression of several proteins and vice versa one protein is influenced by several miRNAs. Their role has been revealed in several physiological and pathological cellular processes including development, cell proliferation, differentiation, apoptosis and tumorigenesis. Therefore, this complex bidirectional link makes the miRNA-miRNA couples as an ideal targets for various therapeutic approaches. In addition, the biogenesis of miRNAs is also regulated by TGF-β, by regulating the maturation process of miRNAs. Members of TGF-β signaling are also targets for miRNAs. Hence auto-regulatory feedback loops between TGF-β and miRNAs influence the fate of tumor cells. Our aim is to review the crosstalk between TGF-β signaling and the miRNA machinery in order to discover bidirectional feedback loops which contribute to the tumorigenesis process of endocrine glands, and to identify potential novel therapeutic targets.

DOI: 10.1530/endoabs.32.S19.1

**S19.2** MicroRNAs in pituitary tumours
Monica Fedele
IEOS-CNR, Naples, Italy.

MicroRNA (miRNAs) are small non-coding RNA molecules that significantly impacted the understanding of cell biology in the last decade. They regulate the expression of 10–30% of all protein-coding gene, thus playing a crucial role in a wide range of biological and pathological processes. Consistently, aberrant miRNA expression has been implicated in numerous human diseases, including pituitary tumours. Different studies analysed the entire miRNA transcriptomes, by microarray and RT-PCR, in normal and neoplastic pituitary tissues, and several aberrant expression patterns of miRNAs in pituitary tumours as compared to normal pituitary have been identified to date. A different miRNA signature has revealed miRNAs to be useful for discrimination of the different pituitary adenoma sub-types, for distinguishing pharmacological treated pituitary adenomas, as well as for differentiation of microadenomas from macroadenomas and carcinomas from adenomas. This is particularly important in the still unsolved issue of distinguishing benign from malignant pituitary tumours prior to metastasis. Based on their differential expression, it is possible to infer the likely role of certain miRNAs in tumor development. In this way a number of studies identified miRNAs controlling pituitary cell proliferation, apoptosis and invasion. Also by identifying the putative or confirmed target of the aberrantly expressed miRNAs has been possible to get significant insight into the role of miRNAs in pituitary tumorigenesis. This is the case of a group of miRNAs, all downregulated in a wide range of pituitary adenomas compared to normal pituitary tissue, which are able to inhibit pituitary cell growth by targeting HMG A proteins in pituitary cells. Indeed, overexpression of HMG A genes is a common feature of human pituitary tumours and it causes pituitary cell cycle dysregulation and development of pituitary adenomas in transgenic mice, thus suggesting that HMG A genes might be considered as specific oncogenes for pituitary cell transformation. Therefore, the restoration of miRNAs targeting HMG A genes or other pituitary oncogenes may represent a new promising therapeutic approach for pituitary adenomas.

DOI: 10.1530/endoabs.32.S19.2

**S19.3** MicroRNAs and gene expression patterns in adrenal tumours
Peter Igaz
Semmelweis University, Budapest, Hungary.

MicroRNA and miRNA expression patterns have been investigated in several studies on adrenocortical tumours and in some reports on pheochromocytomas. These studies are relevant from pathogenic, diagnostic and therapeutic aspects. Under- and overexpressed microRNAs representing tumour suppressor and oncogenic microRNAs have been reported that can be helpful in the diagnosis for differentiating benign and malignant adrenocortical tumours (e.g. miR-503-miR-511, miR-195, miR-483-5p), recurrence-prone and non-recurrent pheochromocytomas (miR-1225-3p) and even benign and metastasing pheochromocytoma (e.g. miR-15a, miR-16, miR-101, miR-183). Differentially expressed miRNAs and microRNAs have been identified that confer prognostic information. Based on miRNA expression patterns, adrenocortical cancer can be subdivided in two groups with different prognosis. Analysis of pathways affected by miRNAs and microRNAs has revealed several potentially druggable pathomechanisms e.g. mTOR in adrenocortical tumours, Notch-signaling in pheochromocytomas. Since the drug repertoire for treating adrenocortical cancer and malignant pheochromocytoma is rather limited, these novel bioinformatics approaches might be of great relevance for deciphering novel pathways. By network analysis, we have found the underexpression of c-MYC in adrenocortical cancer that might be a central pathogenic event. Meta-analysis of adrenocortical tumour genomics data revealed three major pathomechanisms including: i) damage of cell cycle, ii) retinoic acid signaling via retinoic X receptor, iii) immune alterations. Based on these observations, we in vitro studies on 9-cis-retinoic acid in the adrenocortical cancer cell line NCI-H295R have shown the inhibition of growth and hormone secretion, and robust changes in gene expression patterns. 9-cis-retinoic acid also inhibited tumour growth in vivo in a xenograft model that might raise its potential applicability in the treatment of adrenocortical cancer. These findings may pave the way for novel diagnostic and even individualized treatment protocols.

DOI: 10.1530/endoabs.32.S19.3

**New mechanisms of energy balance**

**S20.1**

Abstract unavailable.

DOI: 10.1530/endoabs.32.S20.1

**S20.2**

Programming of host metabolism by the gut microbiota
F Backhed
Sweden.

The gut microbiota has co-evolved with its mammalian host and is an important factor that contributes to host metabolism. Metagenomic analyses of stool samples from patients have revealed that the gut microbiota is altered in these metabolic diseases and germ-free mice are protected against disease development. Thus, the gut microbiota has been implicated as a causative, or contributing, factor to obesity, diabetes as well as cardiovascular disease. By using germ-free and conventionally raised mice we have demonstrated that the gut microbiota modulates obesity and diabetes. Furthermore the gut microbiota is in close interactions with enterendocrine cells in the gut and may affect their function through signaling by G-coupled receptors. Effects on gut microbiota on selected gut derived hormones will be discussed.

DOI: 10.1530/endoabs.32.S20.2

**S20.3**

Abstract unavailable.

DOI: 10.1530/endoabs.32.S20.3

**Multi-centre pituitary studies**

**S21.1**

New classification of pituitary tumours based on the hypopronos data set
Gerald Raveort1,2
1 Hospices Civils de Lyon, Lyon, France; 2 INSEERM, UMR-S1028, Lyon Neuroscience Research Center - Université Lyon 1, Université de Lyon, Lyon, France.

Endocrine Abstracts (2013) Vol 32
Pituitary endocrine tumours are currently classified by histological, immunocytochemical and numerous ultrastructural characteristics but without prognostic clinical correlations. We investigated the prognostic value of a new clinicopathological classification with grades based on invasion and proliferation, the components of tumour behaviour.

This retrospective multicentric case-control study comprised 410 patients who had surgery for a pituitary tumour with long-term follow-up. Using pituitary magnetic resonance imaging for diagnosis of cavernous or sphenoïd sinus invasion, immunocytochemistry; markers of the cell cycle (Ki-67, mitoses and p53), the tumours were classified according to size (micro, macro and giant), type (PRL, GH, FSH/LH, ACTH and TSH) and grade (grade 1a: non-invasive; 1b: non-invasive and proliferative; 2a: invasive; 2b: invasive and proliferative; and 3: metastatic). The association between patient status at 8 years follow-up and age, sex, and classification was evaluated by two multivariate analyses assessing disease-free or recurrence/progression-free status.

At 8 years after surgery, 195 patients were disease-free (controls) and 215 patients were not (cases). In 125 of the cases the tumours had recurred or progressed. Analyses of disease-free and recurrence/progression status revealed the significant prognostic value ($P < 0.001; P < 0.05$) of age, tumour type, and grade across all tumour types and for each tumour type. Invasive and proliferative tumours (grade 2b) had a poor prognosis; with an increased probability of tumour persistence or progression of 25% or 12-fold respectively compared to non-invasive tumours (grade 1a).

This new, easy to use clinicopathological classification of pituitary endocrine tumours has demonstrated its prognostic worth by strongly predicting the probability of post-operative complete remission, or tumour progression and so could help clinicians choose the best post-operative therapy.

**DOI:** 10.1530/endoabs.32.S21.1

**S21.2 Lessons from the Liège Acromegaly Survey (LAS)**

Patrick Pettrossians1, Sabina Zacharieva2, Philippe Chanson3, Sebastian Neggers4, Thierry Brue5, Anamaria Colas6, Anna-Lena Hulting7, Brigitte Delemere8, Vaclav Hana9, Gunter Stalla10, Francesco Minuto11, Marie-Lise Jaffrain-Rea12, Davide Carvalho13, Carmen Fajardo Montanana14 & Albert Beckers1

1 CHU de Liège, Liège, Belgium; 2 Department of Pituitary and Adrenal Diseases, Medical University of Sofia, Sofia, Bulgaria; 3 CHU de Bruxelle, Paris, France; 4 Department of Internal Medicine, Erasmus University, Rotterdam, The Netherlands; 5 CHU Timone, Marseilles, France; 6 Department of Clinical and Molecular Endocrinology and Oncology, University of Ferrero II, Naples, Italy; 7 Karolinska Institute, Stockholm, Sweden; 8 CHU de Reims, Reim, France; 9 Charles University, Prague, Czech Republic; 10 Max Planck Institute, Munich, Germany; 11 Endocrinology Unit, University of Genova, Genova, Italy; 12 Department of Experimental Medicine, University of L’Aquila, L’Aquila, Italy; 13 Centro Hospitalar Sao Joao, Porto, Portugal; 14 Hospital Universitario de La Ribera, Valenci, Spain.

The Liège Acromegaly Survey is a cross-sectional study on acromegalic patients, developed as an in-house tool in Liège, then extended to other European participating centers. The database differentiates itself from national and multinational registries by adopting a goal oriented approach and it was conceived following a list of open questions on acromegaly. After an initial test run in Liège, the database installation started on mid-March 2010. Thirteen other European centers joined the project. At this time, 3050 patients from fourteen centers were included.

Sex ratio (MF) was 1397/1653 (0.85) with strong differences between centers (Porto: 0.43, Valencia: 1.4). Median age at diagnosis was 45.1 and the male population younger than the female (medians: $M = 43.4, F = 46.2, P < 0.001$). When looking at patients’ age and the year of diagnosis, a trend toward an aging of the population was observed with more older patients getting diagnosed with time.

Median duration of disease before diagnosis was 5 years whenever estimation was possible. Acromegaly was suspected in 43% of cases by endocrinologists, in 16% of cases by an internist from different specialities and in 17% of cases by family doctor. Dysmorphia appears as the main sign leading to diagnosis. At diagnosis, glucose levels in non-diabetic patients, hemoglobin concentrations and red blood cell count correlated with IGFI levels but not GH, suggesting that IGFI values are a better representation of the activity of acromegaly than GH.

In summary, the LAS was conceived as a tool to answer a number of questions on the subject of acromegaly. By concentrating on these specific points and recording data from a more than 3000 patients, this database seems to be able to highlight a number of aspects not addressed before.

**DOI:** 10.1530/endoabs.32.S21.2

**S21.3 Lessons from the European Cushing’s registry (ERCUSYN)**

Webb Susan

Hospital S Pau and CIBERER 747, UAB, Barcelona, Spain.

ERCUSYN owned by ESE, was set up in 2007 with European funding for 3 years. Sustainability has been achieved by agreements with pharma, and generous support from funding partners and Lohmann and Birkner GmBH, who established and maintained the on-line registry and web (www.ercusyn.eu).

On-line brochures for patients and physicians are available in different languages, as well as details on >50 participating centres in 28 European countries. By 2012 over 800 patients are included. Data definitions in detailed guidelines are available on-line. Ethical and legal considerations respecting individual requirements in each centre or country have been introduced.

ERCUSYN has evidenced a heterogeneous clinical presentation of CS, depending on gender and aetiology, and confirms long delays between onset of symptoms and diagnosis, with many specialists consulted who often missed the correct diagnosis. Morbidity at diagnosis is high, with low bone mass, especially in men, and impaired quality of life. Less than half the cohort was actively working, despite a mean age of 44 years. So there is great potential for improvements in the delay to diagnosis, with obvious beneficial consequences both for patients and for the health care systems, due to long-term consequences of delayed diagnosis and increased morbidity.

ERCUSYN represents the largest prospective collaboration of CS in Europe, with potential for improving the care of patients, and may be used as a rare disease registry for new orphan drugs to be evaluated. It can be liaised to the European Medicines Agency-regulated, industry-required post-marketing surveillance studies, to follow safety and efficacy in the long-term outcomes in clinical practice conditions. Through the ESE this network may be used to disseminate information and encourage further interaction between endocrinologists across Europe.

Reference


**DOI:** 10.1530/endoabs.32.S21.3

**Improving diagnosis of primary aldosteronism**

**S22.1 Genetics of primary aldosteronism**

Felix Beuschlein

University Clinic Munich, Munich, Germany.

Excessive autonomous aldosterone secretion by the adrenal gland, so called primary aldosteronism (PA), causes drug-resistant and often life threatening arterial hypertension accompanied by severe hypokalemia. Long-term consequences include increased risk for stroke, myocardial infarction and atrial fibrillation. PA is present in up to ~10% in referred patients and 7% in primary care, but as high as 20% in patients with resistant hypertension. The early detection of PA has clear impact on clinical outcome and survival, given the major cardiovascular adverse effects of aldosterone excess, which are independent of blood pressure, and predict outcome following surgical.

With an increasing pace genetic mechanisms have been identified that contribute to autonomous aldosteronism secretion. These include both familial forms as well as acquired somatic cases which partly overlap. Familial hyperaldosteronism type I (FH-1), also called glucocorticoid suppressible aldosteronism, is characterized by early and severe hypertension with biochemical abnormalities of PA and production of hybrid steroids. Fusion of the promoter region of CYP11B2 to the coding region of CYP11B1 produces a chimeric gene, with activity of aldosterone synthase, but regulatory specificity of that of 11β-hydroxylase, which results in the synthesis of aldosterone under control of ACTH. FH-2 has an autosomal dominant mode of inheritance with a variable phenotype including APA and BAH acquired somatic cases which partly overlap. Familial hyperaldosteronism type II (FH-2), also called glucocorticoid insensitive aldosteronism, is characterized by manifestation of CS in young patients and confirms long delays between onset of symptoms and diagnosis, with many specialists consulted who often missed the correct diagnosis. Morbidity at diagnosis is high, with low bone mass, especially in men, and impaired quality of life. Less than half the cohort was actively working, despite a mean age of 44 years. So there is great potential for improvements in the delay to diagnosis, with obvious beneficial consequences both for patients and for the health care systems, due to long-term consequences of delayed diagnosis and increased morbidity.

ERCUSYN represents the largest prospective collaboration of CS in Europe, with potential for improving the care of patients, and may be used as a rare disease registry for new orphan drugs to be evaluated. It can be liaised to the European Medicines Agency-regulated, industry-required post-marketing surveillance studies, to follow safety and efficacy in the long-term outcomes in clinical practice conditions. Through the ESE this network may be used to disseminate information and encourage further interaction between endocrinologists across Europe.

Reference


**DOI:** 10.1530/endoabs.32.S21.3
Primary aldosteronism is the most common form of secondary hypertension. The detection of primary aldosteronism is of particular importance, because it provides an opportunity for a targeted treatment (surgical for unilateral forms and medical with mineralocorticoid receptor antagonists for bilateral forms). PA diagnosis comprises screening, confirmation testing and subtype diagnosis. Guidelines recommend that all patients for whom the surgical treatment is practicable and desired should undergo adrenal vein sampling (AVS) as the gold standard to differentiate unilateral from bilateral adrenal disease. AVS is practicable and desired should undergo adrenal vein sampling (AVS) as the gold standard to differentiate unilateral from bilateral adrenal disease. AVS offers a new tool to improve the performance of AVS. We recently assessed the impact of differing criteria for successful cannulation and lateralization on reproducibility of subtype diagnosis and also the effect of ACTH stimulation. The use of permissive cannulation success criteria can lead to significant numbers of patients being given a definitive subtype diagnosis when stricter criteria would have led to the study results being rejected or interpreted with great caution; unfortunately, permissive criteria are associated with a low reproducibility of the diagnosis. Furthermore, we showed that ACTH infusion may be of help for those centers with a low rate of cannulation and perform at least as well as the unstimulated protocol for final diagnosis of PA subtypes. The possibility of performing adrenalectomy in some selected PA patients without AVS and the necessity of having contralateral suppression of the aldosterone secretion from the adrenals, is still a matter of discussion.

Endocrine disruptors

There are robust data from all parts of the World that the incidence of testicular germ cell cancer, which is often associated with dysgenesis and poor spermatogenesis in adjacent ‘normal’ testicular tissue, has been increasing during the past 50 years. There is also evidence of widespread poor semen quality among young men in European countries, where there also have been reports on declining semen quality. Although the latter findings have been subject to controversy, recent large studies of young men from Denmark, Germany, Spain, France, Finland and Japan have shown that 10–15% of the men had sperm concentrations at levels indicating a high risk of need of assisted reproduction in case they wanted to father a child, and an even larger group of young men in these countries seem to be at risk of a prolonged waiting time to pregnancy. In addition, cryptorchidism and hypospadias remain among the most common congenital abnormalities among boys. These trends taken together with recent reports, showing that 8% of birth cohorts are now born after assisted reproduction, indicate that male infertility may significantly contribute to the decline in fertility rates seen in Europe and many Asian countries. A hypothesis will be presented that modern lifestyle with its wide exposure to endocrine disruptors may play a role together with adverse effects of smoking and obesity.

Male reproductive health and endocrine disrupters

Niels E Skakkebaek
University Department of Growth and Reproduction, Rigshospitalet, Copenhagen, Denmark.

Bisphenol A (BPA) is a chemical often integrated in impact-resistant plastics and surface coatings in canned foods as well as screw-on caps and cashier receipts. BPA is either intentionally added or appear as a consequence of recycling in materials with food contact, which leaves consumers at risk of exposure. BPA has known endocrine disrupting effects and is suspected to be a contributing factor in disorders such as overweight, diabetes, cardiovascular diseases, and behavioral changes in children. Therefore, developing alternatives to BPA is important. The aim of this study was to characterize the toxicological profile of BPA and five analogs, BBP, BPE, BPF, BPS, and 4-cumyl phenol with focus on general toxicity and endocrine disrupting potential. The investigation was conducted by performing a comprehensive quantitative structure activity relationships (QSAR) modeling with respect to a series of adverse human effects, including acute oral toxicity, local irritation, cardiotoxicity, endocrine disruption, reproductive toxicity, genotoxicity, and cancer. Their metabolism via three key cytochrome P450 enzymes and the pregnane X receptor was also evaluated. The toxicological profile of the six bisphenols were supplemented with and compared to data obtained from experimental cell-based assays covering interferences with the androgen, estrogen, PPARγ, and aryl hydrocarbon receptors and interferences with steroidal sex hormone synthesis. Overall, the qualitative profile was in general similar. However, important quantitative differences in potency and efficacy appeared. Work is in progress to reach the overall conclusions.

Overall, the qualitative profile was in general similar. However, important quantitative differences in potency and efficacy appeared. Work is in progress to reach the overall conclusions.

Endocrine Abstracts (2013) Vol 32
Redefining our understanding of the causes of obesity

**S24.1**

**Abstract unavailable.**

DOI: 10.1530/endoabs.32.S24.1

**S24.2**

Social stress, obesity and type 2 diabetes

Alessandro Bartolomucci
University of Minnesota, Minneapolis, Minnesota, USA.

Chronic stress, low socioeconomic status and ingestion of hypercaloric food are all recognized risk factors for obesity, metabolic syndrome (MetS) and type 2 diabetes (T2D). Given the complexity of these metabolic processes and the unavailability of animal models, there is poor understanding of their underlying mechanisms. We established a model of chronic psychosocial stress (CPS) in which animals of low social rank (subordinates, SUB) are vulnerable to weight gain while animals of high social rank (dominants, DOM) are resilient. Recent data will be discussed demonstrating that social status and genetic predisposing factors interact with the nutritional environment to establish individual vulnerability to stress-induced metabolic disorders. Firstly we demonstrated that animals exhibiting high rank (DOM) that are hyperactive and show sympathetic hyperactivity, are fully protected from the development of metabolic disorders when fed both a standard and a high fat diet, despite being hyperphagic. Secondly, we demonstrated that SUB mice fed a standard diet exhibited features of MetS and downregulation of the insulin pathway downstream of IRS and PPARs in liver and skeletal muscle as well as complex changes in lipid metabolism facilitating fat deposition and in WAT. Furthermore, while mice to hypercaloric diet induced the development of glucose intolerance and insulin resistance. Similarly, subordinates stress aggravated glucose intolerance in the diabetic db/db strain of mice. Overall, we demonstrated a robust stress- and social status-dependent effect on the development of MetS and T2D and provided insights on the underlying molecular mechanisms. Our results are reminiscent of, and provide a model for, the effect of the individual socioeconomic status on human health.

DOI: 10.1530/endoabs.32.S24.2

**S24.3**

Ambient temperature and other environmental factors in obesity

Fiona Johnson & Jane Wardle
University College London, London, UK.

Discussion of environmental factors in the development and maintenance of obesity has overwhelmingly focused on the effects of an energy-dense and plentiful food supply and an environment conducive to physical inactivity. In recent years, however, an increased understanding of epigenetics has led to an explosion of interest in the mechanisms through which environmental exposures can exert an influence on energy intake and energy expenditure. Upward trends in domestic winter indoor temperatures is one such influence. Plausible causal mechanisms have been suggested for an effect of reduced exposure to mild cold on population increases in obesity. Experimental studies confirm that human energy expenditure is associated with temperature exposures within the range relevant to indoor heating trends, and the existence of variable amounts of cold-activated brown adipose tissue in adult humans has raised the possibility that thermogenic capacity might be adversely affected by reduced seasonal cold exposure. While these pathways are plausible their validity has not yet been demonstrated in free-living humans. As with other putative environmental factors, translating laboratory research to a real world setting presents a substantial challenge and there are many outstanding questions around the triggering of biological and behavioural compensation mechanisms. Nonetheless the study of the role of environmental factors in body weight raises exciting possibilities for novel public health strategies to address obesity.

DOI: 10.1530/endoabs.32.S24.3

Rare metabolic bone disease

**S25.1**

Paget’s disease of bone: how to treat and monitor patients

William D Fraser
Norwich Medical School University of East Anglia, Norwich, UK.

Paget’s disease of bone (PDB) is the second commonest bone disease. The original disease description in 1876 by Sir James Paget remains an incisive, accurate report of the pathophysiology of PDB, which is characterised by focal regions of increased bone remodelling with initial excessive bone resorption and osteolytic lesions followed by long term increased bone formation and sclerosis. The majority of patients are elderly, many are asymptomatic. Those that are referred to hospital are usually symptomatic with bone pain, skeletal deformity, pathological fractures, neurological symptoms and deafness. There is marked geographical variation in PDB with the highest prevalence/incidence in the UK, particular North West England. Recent studies in the UK and New Zealand have suggested that there is a decline in the prevalence and severity of PDB and a gradual decrease in concentration of total ALP at presentation. Measurement of new biochemical markers of bone metabolism have failed to establish an obvious successor to total ALP in terms of the cost-benefit for the information gained either for diagnosis or follow-up. The modest benefit of bone specific ALP is seen in patients with monostotic (single bone involvement) PDB. The bisphosphonate drugs are the treatment of choice for PDB. IV zoledranate has been assessed compared to oral risedronate in 176 patients with PDB. A single 5 mg infusion of zoledranate produced a more rapid, more complete, and more sustained response in PDB than 2 months treatment with 30 mg risedronate daily. However, questions have been raised regarding the optimal way to treat and assess patients with PDB. A prospective randomised trial of intensive vs symptomatic management (PRISM) of PDB has been performed to investigate how patients should be treated and subsequently extended to include treatment with zoledronate (PRISM-EZ). 1324 entered PRISM with one half receiving increasing analgesia or mild bisphosphonate treatment (symptomatic) and the other group receiving potent bisphosphonates to maintain their total ALP within the reference range (intensive). The primary endpoint was fracture, with secondary endpoints of progression of deafness, requirement for orthopaedic surgery and quality of life. No significant difference was observed between the treatments after an average of 32 months treatment. There is some suggestion from these recent trials that the previous apparent close association between total ALP and disease activity/symptomatology, especially following treatment, no longer holds true and patients should always be assessed clinically including radiological assessment rather than basing treatment purely on biochemical measurements.

References

DOI: 10.1530/endoabs.32.S25.1

Osteogenesis imperfecta

A Kindmark
Sweden.

Osteogenesis imperfecta (OI) is a heterogeneous genetic disorder with a prevalence of 1/15 000 to 1/20 000 individuals. In more than 90% of patients with type I-IV OI, the disorder is due to a dominant mutation in one of the two genes that encode the α chains of collagen type I, COL1A1 and COL1A2. Collagen type I is present in many tissues, and in addition to multiple fractures patients with OI can have dentinogenesis imperfecta, blue sclera, hyper mobile ligaments and skin, hearing loss and increased risk of bruising. Classically, OI is divided into four subtypes, Silence class I-IV, with the addition of three more rare forms. Type I is the most common and is generally mild and non-deforming. Type II is the most severe and is lethal already in the perinatal period, usually due to respiratory insufficiency from multiple thoracic fractures. Type III is severely
deforming and patients often have fractures at birth. Type IV has a clinical range between type I and III and thus is moderately deforming. Recently described types V–VII are rare and lead to a moderate to severe phenotype. The majority of patients with OI have a low BMD. To date there is no cure for OI. Many patients are treated with bisphosphonates, which there is support for in clinical trials, most of these are in children with OI. It is not known if treatment with other osteoporosis drugs would be a better alternative or a perhaps a complement to bisphosphonates in the patient with OI. A therapeutic vision is to use either stem cell therapy or silencing of the mutated genes through RNAi (RNAi).

In this presentation the literature concerning effects of antosteoporotic drugs in adult patients with OI will be revived.

DOI: 10.1530/endoabs.32.S25.2

S25.3

Abstract unavailable.

DOI: 10.1530/endoabs.32.S25.3

Novel technologies and inspiring ideas: From basic endocrine research to clinical practice (European Young Endocrine Scientists (EYES) Symposium)

S26.1

Making a functional thyroid in a dish

Francesco Antonina, Dominika Figińś Kasprzylk, Robert Opitz, Michelina Iacovino, Xiao-Hui Liao, Alexandra Mihaela Dumitrescu, Samuel Reftelli, Kathelijne Peremans, Mario Manto, Michael Kybur & Sabine Costagliola

1 Institute of Interdisciplinary Research in Molecular Human Biology (IRIBHM), Université Libre de Bruxelles, 808 route de Lennik, 1070 Brussels, Belgium; 2 Lillehei Heart Institute and Department of Pediatrics, University of Minnesota, Minneapolis, Minnesota, USA; 3 Department of Medicine, The University of Chicago, Chicago, Illinois, USA; 4 Departments of Pediatrics and Genetics, The University of Chicago, Chicago, Illinois, USA; 5 Department of Veterinary Medical Imaging and Small Animal Orthopaedics, Faculty of Veterinary Medicine, Ghent University, Ghent, Belgium; 6 FNRS, ERASME, Université Libre de Bruxelles, 808 Route de Lennik, 1070 Brussels, Belgium.

During the last decade induced overexpression of defined transcription factors has been shown to have a driving effect on the differentiation of embryonic stem cells (ESCs) into many specific cell types. Nevertheless, the generation of protocols promoting a coordinate self-assembly of differentiated cells into distinct morphological units with also functional properties reminiscent of organs and tissues in vivo are still very sparse. Recently, we have reported the generation of functional thyroid follicles generated from pluripotent stem cells. We show that a transient overexpression of the transcription factors NKX2.1 and PAX9, notably known to play a pivotal role during thyroid organogenesis, in addition to a subsequent treatment with TSH is sufficient to direct murine ESC differentiation into thyroid follicular cells (TFC) and promotes in vitro self-assembly of TFC into three-dimensional follicular structures. In addition to morphological evidences, cells differentiated by this protocol showed significant iodide organification activity, a second hallmark of thyroid tissue function. Importantly, athyroid mice grafted with mESCs-derived thyroid follicles show normalization of plasma T4 levels with concomitant decrease of plasma TSH. Moreover, normalization of body temperature had been observed upon transplantation of thyroid follicles into athyroid mice. Our findings have demonstrated that mESCs can efficiently be differentiated into TFCs that can self-assemble into 3D functional units and finally transplanted in athyroid mice rescuing the hypothyroid state and triggering symptomatic recovery along with the normalization of plasma hormone concentrations. Moreover, the high efficiency of TFC differentiation and follicle morphogenesis in our system will provide an unprecedented opportunity for future studies to decipher regulatory mechanisms involved in embryonic thyroid development. Translating the methodology on human using hESCs and iPSCs could give an important contribution in the understanding of the molecular mechanisms underlying congenital hypothyroidism and thyroid.

DOI: 10.1530/endoabs.32.S26.1

S26.2

Dissecting androgen action: new clues from conditional knockout mice

Lee Smith

MRC Centre for Reproductive Health, University of Edinburgh, Edinburgh, UK.

In males androgens are primarily made by testicular Leydig cells and act as essential regulators of both fetal masculinization and adult reproductive function. The impact of androgens on gene transcription is largely mediated by the androgen receptor (AR), a member of the steroid hormone super-family of ligand activated transcription factors. AR is expressed widely throughout the body, including several key somatic cell-types in the tests. Although we have known for many years that androgens are important regulators of testicular development and function, until recently it has been impossible to determine the specific roles androgens play in each cell-type, and how these cells respond to androgens to ensure correct male development and fertility.

We have exploited conditional gene-targeting of AR using the Cre/lox system to ablate AR function in several key cell-types of the testis, with a view to elucidating the cell-specific roles of androgen-signaling within the testes. These studies have identified novel roles for each cell-type in the promotion of male reproductive function. AR-signaling in Sertoli cells controls post-meiotic germ cell development and LC number. AR-signaling in PTM cells controls all stages of GC development, SC function and LC differentiation. Recent unpublished data suggests AR-signaling in LCs is also important for testicular function, acting via a novel mechanism.

Taken together, these studies provide increasing evidence for the presence of a complex androgen-dependent paracrine signaling pathway within the testis, with each AR-expressing cell-type influencing others to ensure their correct development and function.

DOI: 10.1530/endoabs.32.S26.2

S26.3

Abstract unavailable.

DOI: 10.1530/endoabs.32.S26.3

Steroids in obesity and metabolism

S27.1

11β-Hydroxysteroid dehydrogenase activity and obesity

Jeremy Tomlinson

University of Birmingham, Birmingham, UK.

The global epidemic of obesity and type 2 diabetes has hastened the need to identify novel and efficacious therapies. Based upon parallels with Cushing’s syndrome, tissue specific cortisol excess, independent of circulating levels, has been suggested to have a crucial pathological role and may represent a potential treatment target. In key metabolic target tissues (liver, adipose and muscle), the endoluminal enzyme, 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) catalyses glucocorticoid activation of cortisone to cortisol. Rodent models and translation clinical studies have validated its potential as a therapeutic target and pharmacological and genetic manipulation in rodents have show significant metabolic benefits. Selective 11β-HSD1 inhibitors for use in clinical studies have now been developed and clinical data are emerging. Whilst these compounds appear to improve glycaemic control in patients with diabetes and cause improvements in blood pressure and decrease weight some concerns still remain. The magnitude of the clinical benefit that they confer remains to be fully determined and in most studies they cause activation of the hypothalamic–pituitary–adrenal axis. In addition, they have the potential to limit the endogenous anti-inflammatory actions of glucocorticoids, although clinical data to support this are lacking. Whilst their development has focussed on treating metabolic disease, alternative indications are emerging and further clinical studies are now warranted.

DOI: 10.1530/endoabs.32.S27.1
Metabolic control through glucocorticoid hormones
Stephan Herzig
Joint Research Division Molecular Metabolic Control, German Cancer Research Center, Center for Molecular Biology, Heidelberg University Hospital, Heidelberg, 69120 Heidelberg, Germany.

In the past decades, glucocorticoid (GC) hormones and their cognate, intracellular receptor, the glucocorticoid receptor (GR), have been well established as critical checkpoints in mammalian energy homeostasis. Whereas many aspects in healthy nutrient metabolism require physiological levels and/or action of GC, aberrant GC/GR signalling has been linked to severe metabolic disorders, including obesity, insulin resistance and type 2 diabetes. Consequently, molecular mechanisms within the GC signalling axis have become a major focus in biomedical research, up-to-date particularly focusing on systemic glucose and lipid handling. However, with the availability of novel high throughput technologies and more sophisticated metabolic phenotyping capabilities, as-yet non-appreciated, metabolic functions of GC have been recently discovered, including regulatory roles of the GC/GR axis in protein and bile acid homeostasis as well as metabolic inter-organ communication. This talk will discuss recent advances in GC/GR-controlled energy homeostasis, and summarises findings relevant for basic and translational metabolic research.

DOI: 10.1530/endoabs.32.S27.2

Glucocorticoid-mediated fetal programming in humans
Martijn Finken
VU University Medical Center, Amsterdam, The Netherlands.

There is convincing evidence in animals suggesting a role for prenatal glucocorticoid overexposure in the programming of adult metabolic diseases. Evidence for glucocorticoid-mediated fetal programming in humans often comes from observational studies in preterm babies with variable disease courses, in whom it is difficult to distinguish programming from other effects. Preterm infants early in their neonatal course are subject to stressful and sometimes even critical events, including respiratory distress, intubation and mechanical ventilation, septicaemia, necrotizing enterocolitis, and insertion of venous lines. Obviously, during this period their chances for survival are strongly dependent on the effects of antenatal and/or postnatal glucocorticoid treatment. However, recent studies have shown that once the neonatal threats are resolved, preterm survivors continue to show effects of increased glucocorticoid bioactivity, such as abdominal fat accumulation, glucose intolerance, and raised blood pressure. Several mechanisms with a central role for hypothalamic–pituitary–adrenal axis functioning may underpin these observations. First, subjects who are genetically more sensitive to the effects of endogenous or exogenous glucocorticoids may survive preterm birth easier but are predisposed later to metabolic diseases. Second, extremely stressful insults in early life may induce site-specific alterations in the epigenetic code of the glucocorticoid receptor gene promoter, leading to decreased central feedback suppression, and thus, enhanced stress responsiveness and disease. Third, exposure to glucocorticoids may impact on the development of several organs, depending on the glucocorticoid receptor genotype.

DOI: 10.1530/endoabs.32.S27.3

Autoimmune endocrine disease - Old and new players

Autoimmune thyroid disease
W Wiersinga
The Netherlands.

Graves’ hyperthyroidism (GH) and Hashimoto’s thyroiditis (HI) are the opposite ends of the clinical expression of autoimmune thyroid diseases (AITD). AITD are multifactorial ‘complex’ diseases in which immune responses against thyroid antigens develop in genetic susceptible subjects, provoked by environmental factors. Susceptibility genes include immunoregulatory genes (HLA, CTLA-4, PTPN22, CD4 and FCRL3) and thyroid-specific genes (TSHR and Tg). Environmental factors include ambient iodine intake, stress, smoking, particular drugs (interferon, alentuzumab and HAART), and possibly infections. Endogenous factors (female gender, parity and X-chromosome inactivation) contribute to the risk of AITD. We will focus on new data on the role of environmental factors. Smoking is a well-established risk factor for GH and especially for Graves’ ophthalmopathy. Recent studies provide convincing evidence that smoking to a certain extent protects against HI. Cessation of smoking is associated with de novo development of TPO-Ab, and with a transient increase in the incidence of overt hypothyroidism. The remarkable divergent effects of smoking on GH and HI remain incompletely understood. Alcoholic consumption is associated with a decreased risk of de novo development of TPO-Ab. It also protects against the development of overt GH or HI, independent of smoking behaviour. Selenium deficiency might be involved in the pathogenesis of AITD, but the evidence is less clear. Selenium supplementation in Hashimoto’s thyroiditis decreases serum TPO-Ab in some but not all studies. Selenium concentrations in GH patients are highest in patients who go into remission after a course of antithyroid drugs. Vitamin D deficiency. In a prospective study the de novo development of TPO-Ab was not associated with low serum 25(OH)D. In view of paracrine effects of locally synthesized 1,25(OH)2D and polymorphisms in the vitamin D receptor it is, however, premature to dismiss a role of vitamin D in the pathogenesis of AITD.

DOI: 10.1530/endoabs.32.S27.1

Autoimmune Addison’s disease: new players in diagnosis and treatment
Klaus Badenhoop
Endocrinology and Diabetology, Med. Department 1, University Hospital, Frankfurt/M, Germany.

Addison’s disease is a rare disorder and mostly due to an immune-mediated adrenal destruction similar to the organ specific loss of function in autoimmune hypothyroidism in Hashimoto’s thyroiditis or type 1 diabetes. Adrenal insufficiency occurs thereby as isolated disease or is accompanied by other autoimmune disorders forming the autoimmune polyendocrine syndrome (mostly APS2). A major problem of Addison’s disease is that the diagnosis is often late or may be missed when patients present with acute adrenal crisis. A delay in diagnosis may also impair later quality of life despite optimal steroid substitution. A timely diagnosis is mandatory and therefore adrenocortical function testing should be performed in all patients with suspected Addison’s disease. Patients at risk are those with other autoimmune disorders, in particular women with primary ovarian failure, any with vitiligo or the relatives of patients with Addison’s disease, although the absolute risk is small. Antibodies against the 21-hydroxylase are found in up to 85% of newly diagnosed patients and can be detected prior to manifestation. Such antibody positive individuals must be carefully monitored and – as soon as they become adrenal insufficient- supplemented with hydrocortisone and mineralocorticoids without delay. Although the corticosteroid supplementation pharmacodynamics is a poor mirror of the normal cortisol profile most patients manage their chronic disease in a well adapted manner. There is a subgroup of patients with inadequate results of substitution, a tendency to fall into adrenal crisis and poor quality of life. New modifications of hydrocortisone release may offer an improvement but patients need to be investigated for undetected comorbidities. Vitamin D deficiency is frequently found in patients with Addison’s disease and should be corrected.

Funding
The studies were supported by a grant of the European Union FP7 project Euadrenal (grant no. 201167).

DOI: 10.1530/endoabs.32.S28.2

Hypophysitis
F Kelesstimur
Turkey.

Autoimmune hypophysitis (AH) is characterized by lymphocytic infiltration and eventually destruction of the pituitary tissue. AH accounts for ~1% of pituitary masses and 0.5% of hypopituitarism. Although it has been recognized as an uncommon pituitary disease, its true frequency is not known but certainly underestimated. AH may affect pre- and post-menopausal women, men and children, but most cases are reported in women during reproductive age. AH may be associated with other autoimmune disorders including Hashimoto’s thyroiditis, pernicious anemia, type 1 diabetes mellitus, Graves’ disease, autoimmune
Management of thyroid nodules

S29.1

Molecular analysis of FNAB material
Laura Fugazzola
Department of Clinical Sciences and Community Health, Milan, Italy.

The evaluation of a thyroid nodule is a very common clinical problem and fine needle aspiration biopsy (FNAB) is the only test that can provide a definitive preoperative diagnosis of malignancy. The sensitivity and specificity of FNAB are limited by aspirates that yield insufficient material for definitive diagnosis and those with indeterminate diagnoses, which can account for up to 30–40% of all specimens. The detection of several novel gene mutations in differentiated thyroid cancer (DTC) over the last decade has led to the diagnostic use of these oncocentric alterations to improve FNAB sensitivity and specificity. In recent years, several prospective and retrospective studies have shown that molecular testing of thyroid nodules for a panel of mutations can be effectively performed in a clinical setting and can be useful to improve the diagnosis of malignancy when used as an adjunct to traditional cytology. In particular, either BRAF or RET/PTC, or PAX8/PPARγ or ras, alone or as a panel of oncogenes, have been analyzed in FNAB specimens by diverse Authors. Due to the reported association between BRAF and poorer prognosis, the diagnosis of a BRAF positive nodule can help both to diagnose and to identify those PTC patients who may need more aggressive surgical treatment and vigilant clinical monitoring. Cost-benefit studies showed that molecular testing of indeterminate FNAB results is cost saving predominantly because of a reduction in two-stage thyroectomy and can potentially avoid almost three fourths of currently performed surgeries in patients with benign nodules. In conclusion, the clinical application of molecular techniques to detect mutations in thyroid FNAB samples has been shown to improve the preoperative diagnosis for DTCs and is particularly useful for those tumors that are ‘indeterminate’ by traditional cytological analysis.

DOI: 10.1530/endoabs.32.S29.1

S29.2

Diagnostic pitfalls in fine needle aspiration of thyroid nodules
Sofia Tseleni-Balafouta
First Department of Pathology, University of Athens, Athens, Greece.

Fine needle aspiration (FNA) of thyroid can be confidently enlisted as a primary diagnostic tool in evaluating thyroid nodules to spot cancer, although this confidence should be tempered with awareness of possible diagnostic pitfalls. The sources of pitfalls (toward false positive or false negative results) may lie in sampling, in microscopic interpretation, or even in the clinical evaluation. Nonthyroidal lesions (parathyroid, lymph nodes, and salivary glands) aspirated ‘by mistake’ as thyroid nodules may lead to false diagnoses. Parathyroid adenomas are mostly misdiagnosed as thyroid neoplasms. Sampling in the peritumoral tissue with thyroiditis may miss the neoplasm and lead to a false negative diagnosis. Hashimoto’s disease is a major source for false positive diagnoses based on the sometimes severe reactive epithelial atypia or on the extensive oncocytic metaplasia mimicking oncocytic neoplasm or papillary Ca (PTC). Conversely, neoplastic cells can be obscured by dense lymphoplasmocytic infiltrates. Metaplastic oxyphilic cells in hyperplastic nodules can also be overdiagnosed as neoplastic ones, whereas oxyphilic cells of PTC are sometimes interpreted as metastatic. False negative diagnoses of PTC are sometimes due to the cystic degeneration of the neoplasm and the absence of well preserved neoplastic cells in the smears. Degenerative cell changes may be confusing. The neoplastic nature of highly differentiated PTCs, eventually of the macrofolicular, colloidal rich variant, may be overlooked. Since the cells of medullary Ca may be small with minor atypia, the neoplasm may be underdiagnosed, especially in a colloidal rich background due to admixtures. Sometimes the neoplasm is diagnosed as a lymphoma or a follicular lesion if the specific features are overlooked. A monomorphic pattern of small cells of a poorly differentiated Ca can also be misleading. Paucicellular anaplastic Ca may be missed. Finally, needle tract effects on repeat FNA comprise alterations like reactive follicular or endothelial cells, leading to false positive results.

DOI: 10.1530/endoabs.32.S29.2

S29.3

Follow-up of benign nodules
Enrico Pagini1,2, Irene Misiuchi1,2, Rinaldo Guglielmi1,2 & Giancarlo Bizzarri1,2
1Department of Endocrinology, Regina Apostolorum Hospital, Albano (Rome), Italy; 2Department of Diagnostic Imaging, Regina Apostolorum Hospital, Albano (Rome), Italy.

The majority of thyroid nodules do not need treatment after the exclusion of malignancy or abnormal thyroid function due to the usually slow growth rate of benign thyroid lesions. Clinical and US follow-up should be performed every 1–2 years. A repeated US-FNA is appropriate only in case of relevant nodule growth or suspicious US changes. A minority of benign nodules present a progressive growth that causes local pressure symptoms or patient’s concern. To avoid unnecessary surgery, treatment options include percutaneous ethanol injection (PEI) for recurrent cystic lesions and TSH suppression with levothyroxine (T4) or US-guided thermal ablation for solid nodules. A clinically significant decrease in nodule volume is obtained with T4 only in a minority of patients. Routine use of T4 therapy is not recommended but may be considered, with iodine supplementation, in younger patients from iodine-deficient areas who have small nodules with colloidal features on cytology, or small size nodular goiters with no evidence of functional autonomy. If T4 therapy is not indicated or the nodule grows during the course of treatment, surgery or image-guided mini-invasive procedures may be considered as therapeutic options. PEI is an alternative to surgery for complex nodules with a dominant fluid component. PEI is significantly superior to aspiration alone in reducing nodule volume with a volume decrease >50% in nearly 90% of cases. For solid benign nodules that cause local symptoms or patient’s concern, percutaneous thermal ablation with laser or radiofrequency may be considered as an effective debunking technique. These outpatient procedures are rapid and do not require high-cost devices. US and US-FNA have sharply decreased the rate of diagnostic surgery. US follow-up makes possible an easy and reliable monitoring of benign thyroid nodules. Mini-invasive procedures may further reduce the number of surgical treatments for asymptomatic benign nodules.

DOI: 10.1530/endoabs.32.S29.3

Energy Status and pituitary function

S30.1

Energy status and puberty: novel neuroendocrine regulatory mechanisms
Manuel Tena-Sempere1,2
1Physiology Section, University of Cordoba and IMIBIC, Cordoba, Spain; 2CIBER Fisiopatologia de la Obesidad y Nutricion, Cordoba, Spain.

Reproduction is an energy-demanding function. Accordingly, acquisition of reproductive capacity at puberty is metabolically gated, as a means to prevent fertility in conditions of energy insufficiency. In addition, obesity has been shown to impact the timing of puberty and may be among the causes for the earlier trends of pubertal age reported in various countries, especially in girls but probably also in boys. The metabolic control of puberty in such a spectrum of situations, ranging...
from energy deficit to extreme overweight, is the result of the concerted action of different peripheral hormones and central transmitters that allow the sensing of the metabolic state of the organism and transmit this information to the various elements of the reproductive brain, mainly the GnRH neurons. In this presentation, we will provide a synoptic overview of recent developments that have deepened our understanding of the neuroendocrine and molecular basis for the metabolic control of puberty onset. These include not only the demonstration of the involvement of the hypothalamic Kiss1 system in the control of puberty and its modulation by metabolic cues, but also the identification of the roles of additional transmitters, such as neuropeptide-B and nesfatin-1, and hypothalamic pathways, such as those originating from the ventral pre-mammary nucleus, in the metabolic regulation of puberty. In addition, recent progress in the identification of putative molecular mediators for the metabolic gating of puberty will be reviewed here. All in all, characterization of these novel players and regulatory mechanisms will improve our understanding of the basis of normal puberty, and its eventual alterations in conditions of metabolic stress, ranging from anorexia to morbid obesity.

DOI: 10.1530/endoabs.32.S30.1

S30.2
Energy status and glucocorticoid excess
Emanuela Arvat1, Ioannis Karamouzis2, Rita Berardelli2, Andreae Picu1, Valentina D’Angelo1, Roberta Giordano3 & Ezio Ghigo4
1Division of Oncological Endocrinology, Turin, Italy; 2Division of Endocrinology, Diabetology and Metabolism, Turin, Italy; 3Department of Clinical and Biological Sciences, Turin, Italy.

Glucocorticoids (GC) act at different target tissues by binding two different intracellular receptors, the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR), but their effects vary considerably between subjects, due to a different sensitivity, which is at least partially, genetically determined. GCs are so named based on their actions on carbohydrate metabolism, namely on insulin-dependent processes. In particular, the effect of GC includes increased hepatic glucose production, decreased insulin-dependent glucose uptake into peripheral tissues, breakdown of muscle and fat to provide additional substrates for glucose production, and inhibition of insulin release from pancreatic β cells. On the other hand, they also deeply influence lipid and protein metabolism, thus modifying body composition. In fact, GC excess is characterized by a series of metabolic complications, including abdominal obesity, systemic arterial hypertension, impairment of glucose tolerance, dyslipidemia, and thrombocytic diathesis, which increase cardiovascular risk and mortality rate. Moreover, the detrimental effects of GC on bone mass and turnover as well as the alterations at muscle level, inducing the steroid-mediated myopathy, are known as well. Although there is convincing evidence in the literature that clear hypercortisolism is associated with several metabolic alterations, it is matter of debate whether subclinical GC excess is responsible for the above mentioned abnormalities. Moreover, the remission GC excess usually reduces but does not eliminate these systemic complications and does not completely normalize body composition, thus indicating that the detrimental effects of GC probably last for very long time and that an early diagnosis and cure may, possibly, prevent a negative prognosis of these patients.

DOI: 10.1530/endoabs.32.S30.2

S30.3
Energy status and GH/IGF1 axis
Manuel Gahte1, Jose Cordoba-Chacon1,2, Helen Christian1, Raul Luque1 & Rhonda Kineman1,2
1Research and Development Division, Jesse Brown VA Medical Center, Chicago, Illinois, USA; 2Department of Medicine, University of Illinois at Chicago, Chicago, Illinois, USA; 3Department of Cell Biology, Physiology and Immunology, University of Cordoba, Cordoba, Spain; 4Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, UK.

GH levels decline with age and weight gain and are enhanced in response to nutrient deprivation. Under these circumstances, GH levels are negatively correlated with IGF1 and insulin levels. Since IGF1 and insulin can directly inhibit GH synthesis and release from primary pituitary cells of different species, it is commonly accepted that changes in circulating IGF1 and insulin serve to directly regulate somatotrope function in response to metabolic extremes. However, teasing apart the relative contribution of IGF1 and insulin has been hampered by the fact that: i) the receptors for both hormones (IGFIR and INSR) are structurally/functionally related (i.e. high insulin levels can activate IGFIR), ii) INSR and IGFIR are expressed in the pituitary at comparably high levels; and iii) INSR and IGFIR can interact by forming hybrid receptors or via crosstalk of downstream intracellular signaling pathways, thereby modifying their responses to their respective ligands. In order to evaluate the separate roles of insulin and IGF1 in regulating somatotrope function, we have used the Cre/loxP system to inactivate INSR or/and IGFIR in the somatotropes, in vitro and in vivo. Several novel concepts have emerged from this series of studies. First, although insulin and IGF1 ultimately inhibit GH synthesis/secretion, the in vitro and in vivo mechanisms of action are distinct. Second, somatotrope-specific loss of INSR or/and IGFIR increases GH levels, which cannot be completely compensated for by an intact hypothalamic feedback system, thereby establishing the somatotrope as a primary sensor for changes in circulating insulin/IGF1 levels. Third, under lean conditions, somatotrope-specific loss of INSR has a more profound effect on circulating GH/IGF1 than loss of IGFIR, suggesting insulin plays a primary role in regulating short-term changes in GH secretion. Finally, in the context of diet-induced obesity, the direct effects of insulin (or IGF1) on somatotrope function cannot fully account for the fall in GH levels and therefore, must be driven by insulin-induced changes in hypothalamic function or other systemic factors that act centrally or directly on the somatotrope to reduce GH output.

DOI: 10.1530/endoabs.32.S30.3

Clinical impact of rare mutations in endocrinology

S31.1
Does a new mutation always predict a new disease? Lessons from p27 mutations
Natalia Pellegata
Helmholtz Zentrum München, Neuherberg, Germany.

A few years ago a novel multiple endocrine neoplasia syndrome, named MEN type 4 (MEN4), was discovered thanks to studies conducted on a MEN syndrome in the rat named MENX. Rat and human syndromes are both caused by germline mutations in the Cdkn1b/Cdkn1B gene encoding p27Kip1, a putative tumor suppressor which binds to and inhibits cyclin/cyclin dependent kinase complexes, thereby inhibiting cell cycle progression. MEN4 patients carry heterozygous mutations at various residues of p27Kip1 and present with endocrine lesions mainly belonging to a MEN1-like spectrum. Indeed, the most common phenotypic features in mutation carriers are parathyroid and pituitary adenomas. Recently, germline mutations in p27kip1 were also identified in patients with a sporadic presentation of parathyroid adenomas. In vitro functional characterization of several Cdkn1B sequence variants identified in MEN4 patients, detected impaired activity of the encoded p27Kip1 mutant proteins (e.g. reduced expression, cytoplasmic mislocalization or poor binding to interaction partners). These results indirectly pinpoint the characteristics of the p27Kip1 protein which are critical for tumor suppression. Although the number of MEN4 patients is still very low, the discovery of this syndrome has demonstrated a novel role for Cdkn1B as a tumor susceptibility gene for neuroendocrine tumors. In this lecture, I will review clinical and molecular characteristics of the MEN4 syndrome and the role of p27Kip1 in neuroendocrine tumorigenesis.

DOI: 10.1530/endoabs.32.S31.1

S31.2
Old and new MEN1 mutations
Pr Alain Calender
Department of Medical and Molecular Genetics, University Hospital (HCL), University Claude Bernard Lyon 1, Lyon, France.

Multiple endocrine neoplasia type 1 (MEN1 – OMIM 131100) is considered as the major hereditary syndrome predisposing to multifocal endocrine tumors and a broad spectrum of non-endocrine lesions. Since the cloning of the MEN1 gene in 1997, a large number of studies have shown the large diversity of germline mutations found in patients with a poor genotype–phenotype correlation. Menin, the protein encoded by the MEN1 gene interacts with more than 30 nuclear/cellular factors (menin interacting proteins or MIP’s) involved in major processes of cell life. Among them, Jum2, a negative regulator of the AP1 transcription factor, and mSin3A, a cofactor of chromatin remodeling complexes, are critical determinants of the functional pathway involving menin in the negative regulation of cell proliferation. A powerful network, called Groupe d’étude des Tumeurs Endocrines (GTE) has been initiated in France in 1995 and represents today a comprehensive database on MEN1 patients identified through
Is diabetes a lipid disease?

Abstract unavailable.

DOI: 10.1530/endoabs.32.S32.1

S32.2
Fatty liver disease
Antonia Moschetta
Consortio Mario Negri Sud, University of Bari Medical School, Bari, Italy.

Nonalcoholic fatty liver disease (NAFLD) is becoming a master component of the epidemic of obesity and metabolic syndrome worldwide due to excessive caloric intake. The spectrum of NAFLD ranges from simple fatty liver with benign prognosis to a potentially progressive form, nonalcoholic steatohepatitis (NASH), which may lead to liver fibrosis and cirrhosis resulting in increased morbidity and mortality. Development of hepatic steatosis and its progression to steatohepatitis may be the consequence of dysfunction of several metabolic pathways, such as triglyceride synthesis, VLDL secretion and fatty acid β-oxidation. One main determinant in the pathogenesis of fatty liver seems to be an increment in the serum fatty acid pool. The sources of fat contributing to fatty liver are peripheral TGs stored in white adipose tissue that are driven to the liver in form of plasma non-esterified fatty acids (NEFAs), dietary fatty acids, and hepatic de novo lipogenesis (DNL). The metabolic partitioning of fatty acids between mitochondrial β-oxidation and TG synthesis is critically regulated. In the liver, fatty acid β-oxidation is normally inhibited by formation of the action of insulin, which is the main regulator of DNL due to its direct activation of SREBP1c. Recent studies focused on the transcriptional regulatory proteins that drive mitochondrial biogenesis and oxidative metabolism, lipogenesis and triglyceride (TG) secretion. We will present novel data from tissue-specific mouse models that bolster the concept that a combined non-insulin driven hepatic specific action on lipid synthesis and secretion, as well as, on mitochondrial biogenesis and function could protect against fatty liver and insulin resistance.

DOI: 10.1530/endoabs.32.S32.2

S32.3
Adipose tissue lipolysis and insulin sensitivity
Dominique Langin
Institute of Metabolic and Cardiovascular Disease, Toulouse, France.

When energy is needed, white adipose tissue (WAT) provides fatty acids (FA) for use in peripheral tissues via stimulation of fat cell lipolysis. FA have been postulated to play a critical role in the development of obesity-induced insulin resistance, a major risk factor for diabetes and cardiovascular disease. However, whether and how chronic inhibition of fat mobilization from WAT modulates insulin sensitivity remains elusive. Hormone-sensitive lipase (HSL) participates in the breakdown of WAT triacylglycerol into FA, HSL haploinsufficiency and treatment with a HSL inhibitor resulted in improvement of insulin tolerance without impact on body weight and fat mass in high fat diet-fed mice. Notably, WAT inflammation was not modified. In vivo palmitate turnover analysis revealed that blunted lipolytic capacity is associated with diminution in FA uptake and storage in peripheral tissues of obese HSL haploinsufficient mice. The reduction in FA turnover was accompanied by an improvement of glucose metabolism with a shift in respiratory quotient, increase of glucose uptake in WAT and skeletal muscle and, enhancement of de novo lipogenesis and insulin signalling in liver. In human adipocytes, HSL gene silencing led to improved insulin-stimulated glucose uptake resulting in increased de novo lipogenesis and activation of cognate gene expression. In clinical studies, WAT lipolytic rate was positively and negatively correlated with indexes of insulin resistance and WAT de novo lipogenesis gene expression, respectively. In obese individuals, chronic inhibition of lipolysis resulted in induction of WAT de novo lipogenesis gene expression. Thus, reduction in WAT lipolysis reshapes FA fluxes without increase of fat mass and improves glucose metabolism through cell-autonomous induction of fat cell de novo lipogenesis which contributes to improved insulin sensitivity.

DOI: 10.1530/endoabs.32.S32.3

15th European Congress of Endocrinology 2013
Meet the Expert Sessions
MTE1

What systems biology can do for endocrine research?
Matej Oresic
VTT Technical Research Centre of Finland, Espoo, Finland.

Systems biology views and studies the biological systems in the context of complex interactions between their building blocks and processes. Given its multi-level complexity, metabolic syndrome (MetS) makes a strong case for adopting the systems biology approach. Despite many MetS traits being highly heritable, it is becoming evident that the genetic contribution to these traits is mediated via gene-gene and gene–environment interactions across several spatial and temporal scales, and that some of these traits such as lipotoxicity may even be a product of long-term dynamic changes of the underlying genetic and molecular networks. This presents several conceptual as well as methodological challenges and may demand a paradigm shift in how we study the undeniable strong genetic component of complex disorders such as MetS. The argument will be made that for adopting systems biology approaches to MetS an integrative framework is needed which glues the biological processes of MetS with specific physiological mechanisms and principles and that lipotoxicity is one such framework. The metabolic phenotypes, molecular and genetic networks can be modeled within the context of such integrative framework and the underlying physiology.

DOI: 10.1530/endoabs.32.MTE1

MTE2

Abstract unavailable.

DOI: 10.1530/endoabs.32.MTE2

MTE3

Insulin therapy
Ilhan Satman
Division of Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine, Istanbul University, Istanbul, Turkey.

Insulin replacement therapy is essential for anyone with type 1 diabetes. Most patients with gestational or type 2 diabetes may also require insulin. The goals of insulin therapy are: to achieve optimal glycemic control without causing hypoglycemia or excessive weight gain and to minimize the impact on lifestyle. The therapeutic goals should be individualized according to patient’s age, disease duration, complications, comorbidities, lifestyle, and expected survival. Selection of insulin regimens depends on residual endogenous insulin or insulin resistance, glucose control, and daily activities. The later insulin therapy is initiated, the less likely that target HbA1c will be achieved. Insulin therapy is not without challenges. Patient’s and/or physician’s resistance to insulin need to be overcome. As a consequence, starting and adhering to therapy has been difficult for both sides. Generally insulin analogs are not superior to human insulin in achieving glycemic control. However, the risk of hypoglycemia is lower, and they provide more flexibility.

There is no right way to initiate insulin therapy but there are several options and some guidelines derived from clinical trials. Insulin regimens for type 1 diabetes patients consist of basal-bolus components. The initial dose can be calculated 0.3–0.5 IU/kg per day given as 50% basal and 50% bolus in divided doses before meals. Carbohydrate counting and correction insulin doses may help to achieve better glycemic control. The initial dose for basal insulin in patients with type 2 diabetes is usually 0.2–0.3 IU/kg per day. If glycemic control is not achieved with basal insulin alone, intensification of insulin therapy with addition of a regular or rapid-acting insulin to basal insulin is indicated. Alternatively, a premixed biphasic formulation can be used before breakfast and dinner. Insulin pump therapy may provide more flexible daily life with less frequency of hypoglycemia in most patients with type 1 and in some with type 2 diabetes.

DOI: 10.1530/endoabs.32.MTE3

MTE4

Abstract unavailable.

DOI: 10.1530/endoabs.32.MTE4

MTE5

Current guidelines for the classification of net
Guido Rindi
Institute of Anatomic Pathology, U.C.S.C. Policlinico A. Gemelli, Largo A. Gemelli, 8, 00168 Rome, Italy.

Neuroendocrine neoplasms (NENs) are a variety of neoplastic lesions distributed in most organs and apparatus. The current World Health Organization (WHO 2010) introduced tumor grading (G1–G3) and tumour node metastasis (TNM) staging for class definition. The proposed grading system defines three classes (G1–G3) according to both mitotic count and Ki67 index. Three classes were defined as WHO class 1, neuroendocrine tumor (NET), G1; WHO class 2, NET G2 and WHO class 3, neuroendocrine carcinoma (NEC), by definition G3. The definition of NET equalizes the previous definition of ‘carcinoid’ (typical and atypical as variably utilized in the pathology literature) and of well-differentiated endocrine tumor/carcinoma as from the previous WHO 2000 classification. The WHO 2010 TNM substantially endowed the classification (originally proposed by the European Neuroendocrine Tumour Society (ENETS) with two exceptions in that i) it limits its application to NET G1–G2 (carcinoids) and ii) it shows significant differences for pancreas and appendix TNM definitions. In general a common staging system frame was defined with stage I tumors with limited growth, stage II larger or more invasive tumors, in absence of metastases, stage III tumors invading the surrounding structures or with loco-regional metastases and stage IV implying distant metastases. This classification system was first adopted by the International Union Against Cancer (UICC) and subsequently endorsed by both the American joint Cancer Committee (AJCC) and the WHO. Current oncology guidelines for Neuroendocrine neoplasms are largely based on proliferation fraction and stage to define specific therapeutic options.

DOI: 10.1530/endoabs.32.MTE5

MTE6

New immunotherapy approaches for Graves’ orbitopathy
Mario Salvi 1,2
1Graves’ Orbitopathy Center, Endocrinology, Fondazione Ca’ Granda Ircs, Milan, Italy; 2Department of Clinical and Community Sciences, University of Milan, Milan, Italy.

The role of B-cell in human autoimmune disease have recently been emphasized due to the therapeutic benefit of B-cell depleting therapies. B cells are involved in the production of autoantibodies, CD4+ T-cell activation and control of T-cell function and inflammation, through cytokine production. Although autoantibodies alone may not initiate autoimmune disease, their relationship with the disease course suggests that they are a key factor contributing to the mechanisms of disease pathogenesis. B cells are also important antigen presenting cells? Rituximab (RTX) has been used off-label in various autoimmune disorders and effectively depletes mature and memory CD20+ B cells, but not long-lived plasma cells. This has provided the rationale for the use in Graves’ disease (GD), since blockade of pathogenic autobody generation might induce Graves’ hyperthyroidism remission. Although we suggest caution in proposing RTX as a novel therapeutic tool in this disease, preliminary data collected by us and others show that RTX does significantly affect the inflammatory activity and severity of GO. Recently, we have reported that low dose of RTX (100 mg), about 20-fold less than the commonly administered dose, caused effective peripheral B cell depletion and induced long term remission of GO, without further treatment. The amelioration of GO has not been different from what has been reported with larger doses of RTX. This study is potentially interesting also from the point of view of the safety concerns when using higher doses of a potent immunosuppressive agent like RTX. We envisage that the optimal strategy for controlling the progression of a disease like GO would be to pursue B cell depletion shortly after diagnosis and not solely as additional therapy when standard immunosuppression has failed.

DOI: 10.1530/endoabs.32.MTE6
MTE7

Abstract unavailable.

DOI: 10.1530/endoabs.32.MTE7

MTE8

Abstract unavailable.

DOI: 10.1530/endoabs.32.MTE8

MTE9

Abstract unavailable.

DOI: 10.1530/endoabs.32.MTE9

MTE10

Abstract unavailable.

DOI: 10.1530/endoabs.32.MTE10

MTE11

Abstract unavailable.

DOI: 10.1530/endoabs.32.MTE11

MTE12

Abstract unavailable.

DOI: 10.1530/endoabs.32.MTE12

MTE13

Hypogonadotropic hypogonadism
Taneli Raivio
Helsinki University Central Hospital, Helsinki, Finland.

Patients with congenital hypogonadotropic hypogonadism (cHH; also referred to as idiopathic HH) have inadequately low gonadotropin and sex steroid levels for age without an underlying organic or functional cause. The combination of cHH and deficient sense of smell is called Kallmann syndrome (KS; incidence 1:30,000 in Finnish boys, and 1:125,000 in girls), which is due to misrouting of primitive GnRH neurons in utero from the olfactory placodal area to the developing hypothalamus.

The phenotypic features of cHH are variable. Hallmarks of severe reproductive phenotype include micropenis and/or cryptorchidism, whereas those with a partial reproductive phenotype may show some signs of gonadotropin and sex steroid action. Examples of associated phenotypes include cleft lip/palate, hearing loss, synkinesia, and limb anomalies. Approximately 10% of male cHH patients display reversal of hypogonadotropic later in life after androgen exposure.

Patients with cHH may have family members with cHH, delayed puberty, cleft lip/palate, infertility, cryptorchidism, or hyposmia/anosmia. In clinical examination, special attention should be paid on the stage of puberty, size of the testes, and on the presence of associated phenotypes. Chronic diseases, multiple pituitary hormone deficiency, syndromes, and organic and functional causes of HH should be ruled out. In addition to measurement of gonadotropin and sex steroid levels, Sertoli cell-derived inhibin B and AMH levels together with GnRH and hCG stimulation tests are usually of diagnostic value.

All patients with cHH should be referred to genetic counseling. Currently, 30-40% of cHH patients can be given a molecular genetic diagnosis. Certain phenotypic cues help to prioritize mutation screening. For example, semicircular canal hypoplasia should prompt testing of the CHD7 gene, and patients with anosmia in combination with bimanual synkinesia should be first screened for a mutation in KAL1. Biallelic defects in GNRHR, GNRH1, TAC3, TACR3, KISS1, KISS1R underlie normosmic cHH, and mutations in FGFR1, FGF8, PROKR2, PROK2, or CHD7 have been reported in cHH patients with normal or deficient sense of smell.

DOI: 10.1530/endoabs.32.MTE13

MTE14

Abstract unavailable.

DOI: 10.1530/endoabs.32.MTE14

MTE15

Abstract unavailable.

DOI: 10.1530/endoabs.32.MTE15

MTE16

Diabetic foot disease for endocrinologists
Anthony Coll
Addenbrookes Hospital, Cambridge, UK.

Foot complications are common in people with diabetes. As the incidence of diabetes continues to rise and an increasingly aged population accrue substantial numbers of non-reversible, chronic disease processes, the burden of diabetic foot disease can only grow. Ulceration and amputation are associated with high mortality, reduced quality of life and significant financial cost to both patient and health care provider.

The management of diabetic foot disease is not the preserve of a single specialism, surgical or medical. Rather, there is an absolute requirement for a multi-faceted team to attend to the myriad of pathological processes which are increasingly seen in affected patients. By its very nature endocrinology requires an understanding of how disorders in one system can have ramifications in sites some way distant. Endocrinologists are trained to assess pathophysiology in an integrated and holistic manner, are well

Endocrine Abstracts (2013) Vol 32
used to working in multidisciplinary teams in other aspects of their practice and are therefore well placed to take on an important role at the heart of a service addressing the needs of a fragile patient group. The heterogeneity of the patient population makes definitive guidelines a challenge and the lack of a robust evidence base for interventions can engender a lukewarm response in the face of a pressing clinical need. Using ‘real world’ clinical examples, this session will cover the common clinical presentations of acute foot disease and consider how to utilise the skills and input from all members of the clinical team in tackling and successfully managing this oft neglected area to good effect.

DOI: 10.1530/endobs.32.MTE16
JOE/JME Prize Presentation
Sponsored by Journal of Endocrinology
Enhancing radioiodine uptake in thyroid cancer

JP1

Enhancing radioiodine uptake in thyroid cancer

V E Smith

School of Clinical and Experimental Medicine, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK.

Ablative radioiodine therapy is critical to the treatment of differentiated thyroid cancers and their metastases, and relies on the innate ability of thyroid cells to uptake iodide via the sodium iodide symporter (NIS). As tumours with reduced avidity for radioiodine have a poorer prognosis, it is critical to identify ways to induce NIS activity and hence radioiodine uptake.

Pituitary tumor transforming gene (PTTG) and its interacting partner, PTTG-binding factor (PBF), are proto-oncogenes that are significantly upregulated in thyroid tumours and have been identified as potent repressors of iodide uptake. Higher levels of PTTG and PBF expression are independently associated with early tumour recurrence and an overall poorer disease outcome. Both PTTG and PBF can inhibit NIS transcriptional regulation via an upstream enhancer element (hNUE). NIS can also be post-translationally regulated through an interaction with PBF that internalises it away from its functional localisation at the cell surface. PBF elicits a similar mechanism of post-translational regulation on the monocarboxylate transporter 8 (MCT8), which mediates the secretion of thyroid hormone, suggesting a role for PBF in the overall regulation of thyroid hormone biosynthesis and secretion.

Recent studies have focused on inhibiting NIS repression by PBF. PBF has been identified as a phospho-protein that can bind the proto-oncogene tyrosine-protein kinase Src. Src significantly induces phosphorylation of PBF residue Y174 and, conversely, Src inhibition reduces Y174 phosphorylation. Of direct clinical importance to the treatment of thyroid cancer, Src inhibition entirely overcomes PBF repression of iodide uptake in human primary thyroid cells. Hence, targeting PBF phosphorylation at residue Y174 via tyrosine kinase inhibitors may be a novel therapeutic strategy to enhance the efficacy of ablative radioiodine treatment in thyroid tumours.

DOI: 10.1530/endoabs.32.JP1

Endocrine Abstracts (2013) Vol 32
Endocrine Nurse Symposium
EN1.1
Pre- and post-operative care of the patient undergoing pituitary surgery
Hetty DeVroom
National Institutes of Health, Bethesda, Maryland, USA.

The care of the patient undergoing pituitary surgery is complex and requires detailed knowledge of the underlying diagnosis of the patient. Although the care of the patient is similar with each type of hormonally active tumour, specific knowledge is paramount for a successful post-operative outcome. In this presentation, the medical and surgical management of common pituitary tumours will be discussed. Patients with Cushing’s disease and acromegaly will be highlighted. The pre- and post-operative nursing assessment, surgical resection of tumour, and post-operative management, including common complications will be discussed. At the end of the lecture, the endocrine nurse will have a working knowledge of the care of the patient undergoing pituitary surgery.

DOI: 10.1530/endoabs.32.EN1.1

EN1.2
Pituitary dynamic testing
Nick van der Meij
University Medical Center, Utrecht, The Netherlands.

Due to the pulsatile characteristic of pituitary hormone secretion, its involvement in the acute response to stress and feed-back mechanisms with hormones of peripheral glands, baseline circulating levels of many pituitary hormones may significantly overlap between normal subjects and patients with pituitary disease. Therefore pituitary testing has been widely used for the diagnosis and follow-up of pituitary disease.

For example, provocative tests are frequently used in the diagnosis of adult GH deficiency (GHD), because normal IGF1 levels do not rule out severe GHD. The insulin tolerance test (ITT) is still considered as the test of reference but it should be recognized that other, less bothersome, tests are as reliable as the ITT, for example the GHRH/arginine stimulation test.

The endocrine nurse has an important role in conducting these tests. This role involves more than just administrating the diagnostic agent and blood sampling. Firstly, the endocrine nurse has a job in providing information to the patient about the purpose, adverse effects, and practical execution of the test. Secondly, it is very important that the endocrine nurse observes the patient well and that he/she is able to act quickly and correctly upon complications or problems. The problems that the endocrine nurse may face are divers and require an adequate approach.

The endocrine nurse can take responsibility in writing and updating protocols in collaboration with an endocrinologist. All of this demands knowledge of anatomy and physiology of the endocrine system, knowledge about the various function tests and knowledge about blood sampling techniques and laboratory techniques.

DOI: 10.1530/endoabs.32.EN1.2

EN1.3
Abstract unavailable.

DOI: 10.1530/endoabs.32.EN1.3

EN1.4
GH replacement in adults
Sofia Llana
University College Hospital, London, UK.

GH deficiency in adults is associated with physical, psychological and quality of life impairment. A vast range of treatment options is available for GH and with the right device and adequate education and monitoring, patients report a significant improvement in their quality of life. A holistic approach should be adopted when deciding on a treatment regime for GH, which takes into consideration the patient’s physical/cognitive ability and their social environment.

The Endocrine Nurse has a vital role in selecting the right treatment and monitoring patient’s progress. Biochemical parameters and quality of life questionnaires provide useful information, however, they should be combined with regular consultations, continuing education, and patient’s active involvement in their treatment to provide the best outcome.

At University College Hospital in London we have a caseload of 250 patients on GH. Following diagnosis of GH deficiency, patients are referred to the Endocrine Nurse for treatment initiation and long term monitoring based on an evidence based protocol. A detailed face to face initial consultation ensures that patients receive the right education and information about their treatment and long-term monitoring.

Patients are then transferred to a Nurse-led telephone clinic for six monthly follow ups, although these do not replace their routine face to face pituitary clinic appointments. A recent audit showed that patients on GH monitored in the Nurse-led Clinic report better levels of satisfaction with and adherence to treatment as well as biochemical parameters compared to patients monitored in the community by their General Practitioner. This supports the need for patients on GH to be monitored in a Nurse-led Clinic, although the Endocrine Nurse should be aware of the risk of other team members being de-skilled and should organize regular educational sessions which will provide them with the up to date developments in this area.

DOI: 10.1530/endoabs.32.EN1.4

EN1.5
Abstract unavailable.

DOI: 10.1530/endoabs.32.EN1.5

EN2.1
The role of the endocrine nurse in the care and treatment of children with congenital adrenal hyperplasia and in their transition to the adult service
Margaret Keil
National Institutes of Health, NICHD, Bethesda, Maryland, USA.

Congenital adrenal hyperplasia (CAH) describes a group of autosomal recessive disorders characterized by impaired cortisol biosynthesis. The most common form of CAH is due to 21-hydroxylase deficiency and there is a wide range of phenotypes. The challenge in management of CAH in childhood is promotion of normal growth and development. The morbidities associated with currently available therapeutic regimens are related to glucocorticoid and/or androgen excess, intertwined with the difficulty of achieving a balance between over- or under-treatment. Once linear growth is completed, the management of CAH focuses on coordination of health care and prevention of long-term complications such as obesity, infertility, osteoporosis, and metabolic syndrome.

A multidisciplinary team approach, including endocrinologists (pediatric and adult), endocrine nurse specialists (pediatric and adult), geneticist, urologist, gynecologist, psychologist, social worker, and nutritionist is recommended to optimize the health outcomes of the young adult and their transition to adult service. The endocrine nurse specialist often assumes the role of coordinator in order to facilitate communication between the pediatric and adult teams and the young adult/family to ensure a smooth transition of care, as well as to reduce fragmentation of care. The role of endocrine specialist nurses also includes education and advice to the young adult about achieving independence in the care of their medical condition, which may include planning for emergency care and travel, and moving away from parental home. In addition the role of the nurse involves ongoing assessment of response to changes in treatment, discussion about issues related to sexuality, and education and counseling about risk taking behaviors. Future studies are needed to identify effective intervention models for health promotion in the care of the young adult with CAH that include outcome measures such as quality of life, patient satisfaction, and cost effectiveness.

DOI: 10.1530/endoabs.32.EN2.1
Management of CAH in adults
Richard Ross
University of Sheffield, Sheffield, UK.

CAH is the commonest inborn endocrine disorder and associated with significant morbidity. The health status of CAH adult patients has recently been reported by the UK Congenital adrenal Hyperplasia Adult Study Executive, CaHASE (Arlt et al. JCEM 2010 95 5110–5121). Compared to the health survey for England, metabolic abnormalities were common in adult patients with CAH: obesity (41%), hypercholesterolemia (46%), insulin resistance (29%), osteopenia (40%), and osteoporosis (7%). HR-QOL (SF-36) showed significant impairment similar to scores in heart failure. The CAH patients were taking different glucocorticoid therapies at various doses (n=196): hydrocortisone (n=25M, 26W), prednisolone (n=21M, 67W), dexamethasone (n=15M, 22W), or combination therapy (n=4M, 16W). The CaHASE group have hypothesised that steroid dose mediates some adverse metabolic outcomes. ANOVA and univariate regression analysis only showed weak correlations (r<0.2) between prednisolone equivalent dose and SBP and DBP, HDL-cholesterol and HOMA-IR. However, using principal component analysis (PCA), it was identified that disease control factors, BP and mutation severity are associated with both the choice and total dose of glucocorticoid prescribed. Studies, independent of CaHASE, have examined the development of a modified release formulation of hydrocortisone, Chronocort, for the treatment of adults with CAH. Chronocort, in dexamethasone suppressed normal individuals, is capable of recreating the physiological rise in overnight cortisol levels and in adult patients with CAH improved control of morning 17-hydroxyprogesterone compared to immediate release hydrocortisone. In conclusion, health status in adults with CAH is significantly impaired and Chronocort represents a foundation for future drug development in the pursuit of physiological cortisol replacement. CaHASE is grateful to the Society for Endocrinology for management of the project and The Clinical Endocrinology Trust for financial support.
DOI: 10.1530/endoabs.32.EN2.2

A patient’s perspective of CAH: the importance of care
Rick James
None, N/A, UK

Having been diagnosed with congenital adrenal hyperplasia at the age of 5. I have been lucky enough to turn out as an adult with minimal impact from the condition, and lead a broadly normal life. This brief talk intends to provide a brief diagnostic background for my case, but mainly to focus on the lasting benefits that medical professionals can provide to a patient.

When dealing with children, the importance of providing factual education to the parents is broadly common place, but beyond facts, what about the attitude to a condition? Parents’ fears of harm coming to their children, and patients’ lack of understanding over consequences to low adherence to medication regimes can undermine excellent treatment at any age. The importance of the support is no less than the importance of medicinal treatment.

This talk is largely subjective, although based on my own experiences. Hopefully it will give some food for thought about how, even though contact time with a patient will often be <1% of the time in a year, the importance of care can provide a lasting benefit for 100% of the year.
DOI: 10.1530/endoabs.32.EN2.3

Abstract unavailable.

Incorporating research in to the role of the endocrine nurse: an example from my practice
C Follin
Department of Endocrinology, Lund University, Lund, Sweden.

Incorporating research findings into clinical practice is the primary reason why research is done. The main goal is to offer evidence-based care to the patients. Retaining the nursing findings and integrating them into the healthcare will provide an injustice to the nursing profession.

Obtaining support from the leader team is important in a sucessful research nursing project.

We also need resources, time, training and energy if we will create an environment in which nursing research is accepted and necessary. Further, keeping research projects in a short time-frame will help maintain motivation and attention among the patients, as well as the health care actors. Results will be seen faster and satisfaction fulfilled from completing a task and seeing the light at the end of the tunnel.

At the Department of Endocrinology in Lund, Sweden, we have performed a research project in cranially irradiated survivors of childhood acute lymphoblastic leukemia (ALL) with pituitary insufficiency. The survival after childhood ALL has improved dramatically and late complications are common after cranial radiotherapy, with cardiovascular mortality as the leading cause of death. We have shown that 90% of cranially irradiated adult survivors of childhood ALL have GH deficiency, and that GH therapy decreases the risk of cardiovascular complications. Twenty years after diagnosis we also recorded prolactin (PRL) insufficiency and a high prevalence of lactation failure. Further, we have shown a central adrenal insufficiency among 58% of our ALL survivors, and a decrease in bone mineral density z-scores, indicating a future risk of osteoporosis. We have implemented the research results into clinical practice at our department and we offer the survivors a multidisciplinary surveillance with specific treatments and recommendations. We are now planning to implement the program at all University Hospitals in Sweden.

DOI: 10.1530/endoabs.32.EN3.2

Endocrine nursing in Denmark
H. Høi
Denmark.

Introduction
A summary of developments in nursing over the past years in the specially endocrinological diseases. The presentation will respectively be in a nursing perspective and in a patient perspective. Furthermore it will be based on nursing for patients with acromegaly, Cushing’, Addison’ and pheochromocytoma.

The results show a change in the quality of medical care for these groups of patients. It emerged from the nurse’s closer contact with patients in the investigation phase and the course of treatment. The nurse’s increased knowledge of the patient categories has made this possible.

Patient’s involvement and the possibility of close telephone contact has given patients greater peace of mind and quality of life.

DOI: 10.1530/endoabs.32.EN3.1

A summary of developments in nursing over the past years in the specially endocrinological diseases. The presentation will respectively be in a nursing perspective and in a patient perspective. Furthermore it will be based on nursing for patients with acromegaly, Cushing’, Addison’ and pheochromocytoma.

The results show a change in the quality of medical care for these groups of patients. It emerged from the nurse’s closer contact with patients in the investigation phase and the course of treatment. The nurse’s increased knowledge of the patient categories has made this possible.

Patient’s involvement and the possibility of close telephone contact has given patients greater peace of mind and quality of life.

DOI: 10.1530/endoabs.32.EN3.1

Incorporating research in to the role of the endocrine nurse: an example from my practice
C Follin
Department of Endocrinology, Lund University, Lund, Sweden.

Incorporating research findings into clinical practice is the primary reason why research is done. The main goal is to offer evidence-based care to the patients. Retaining the nursing findings and integrating them into the healthcare will provide an injustice to the nursing profession.

Obtaining support from the leader team is important in a succesful research nursing project.

We also need resources, time, training and energy if we will create an environment in which nursing research is accepted and necessary. Further, keeping research projects in a short time-frame will help maintain motivation and attention among the patients, as well as the health care actors. Results will be seen faster and satisfaction fulfilled from completing a task and seeing the light at the end of the tunnel.

At the Department of Endocrinology in Lund, Sweden, we have performed a research project in cranially irradiated survivors of childhood acute lymphoblastic leukemia (ALL) with pituitary insufficiency. The survival after childhood ALL has improved dramatically and late complications are common after cranial radiotherapy, with cardiovascular mortality as the leading cause of death. We have shown that 90% of cranially irradiated adult survivors of childhood ALL have GH deficiency, and that GH therapy decreases the risk of cardiovascular complications. Twenty years after diagnosis we also recorded prolactin (PRL) insufficiency and a high prevalence of lactation failure. Further, we have shown a central adrenal insufficiency among 58% of our ALL survivors, and a decrease in bone mineral density z-scores, indicating a future risk of osteoporosis. We have implemented the research results into clinical practice at our department and we offer the survivors a multidisciplinary surveillance with specific treatments and recommendations. We are now planning to implement the program at all University Hospitals in Sweden.

DOI: 10.1530/endoabs.32.EN3.2

Endocrine Abstracts (2013) Vol 32
There is currently no set framework against which an adult endocrine nurse specialist can measure their practice. In December 2010, a working party was formed by the nurse committee of the Society for Endocrinology to draw up a competency framework for Adult Endocrine Nurses. The working party comprised of eight experienced endocrine specialist nurses with a mixture of adult and paediatric experience working in both NHS and private settings. The framework was developed over a 2-year period.

Nine competencies were formulated, chosen because they are the most common group of conditions cared for in a nursing capacity by Endocrine specialist nurses. These were for acromegaly, Cushing’s syndrome, dynamic function testing, GH deficiency, hypogonadism, hypopituitarism, steroid replacement therapy, thyroid, and transitional care of the young adult.

These competencies are divided into three sections: competent, proficient, and expert with each of the levels encompassing the previous level. The working party discussed the skills, knowledge and aptitude required for each topic at each level and how to demonstrate the level of expertise reached and to set targets for future development. We recognised that endocrine nurses may have different levels of expertise for each competency and may not be working at the same level on all of these competencies at a given time. Whilst the document suggests a time scale for development of the nurse from novice to expert it is left to the individual departments to decide.

The framework can be adapted to suit service requirement and can be used for appraisals to set targets and objectives as well as monitoring progress.

This is a first part of an ongoing process where further competencies will be added as the document is used and evaluated.

DOI: 10.1530/endoabs.32.EN3.3
Oral Communications
Pituitary & Molecular Endocrinology

OC1.1 – ESE Young Investigator Award

The consequences of changing endogenous GH/IGF1 levels on carcinogenesis of mammary gland tumorigenesis are dependent on metabolic status in mice

Manuel D Gahete1, José Córdoba-Chacón1, Daniel D Lantvit1, Francisco Pérez-Jimenez2, José López-Miranda3, Steven M Swanson4, Justo P Castaño5, Raúl M Luque5 & Rhonda K Dungan1

1Research and Development Division, Jesse Brown Veterans Affairs Medical Center and Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, University of Illinois at Chicago, Chicago, IL, USA; 2Department of Medicine, University of Massachusetts Medical School, Worcester, MA, USA; 3Department of Cell Biology, Physiology and Immunology, University of Cordoba, Reina Sofía University Hospital, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), and CIBER Fisiopat, Córdoba, Spain; 4Lipid and Atherosclerosis Research Unit, IMIBIC, Reina Sofía University Hospital, University of Cordoba, and CIBERObn, Avda. Menéndez Pidal, Córdoba, Spain; 5Department of Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago, Chicago, IL, USA.

Introduction

GH and IGF1 are thought to promote breast carcinogenesis as circulating levels of GH/IGF1 are positively correlated with breast cancer risk in epidemiologic studies, and mouse models with developmental GH/IGF1 deficiency or resistance are less susceptible to breast cancer development. However, no studies have shown that high levels of circulating GH/IGF1 can promote mammary tumorigenesis. In this study, two mouse models with elevated or reduced levels of endogenous GH (HiGH and adult-onset GH-deficient (AOiGHD) mice respectively) were used to test the hypothesis that changes in endogenous GH/IGF1 levels can alter the sensitivity of the mammary gland to tumor formation under normal or diet-induced obese conditions.

Methods/design

8–10-week-old chow-fed HiGH, AOiGHD and their respective controls were treated with DMBA (500 mg/10 g BW) for 5 consecutive weeks and the development and progression of mammary gland tumors monitored for 24-weeks. Additionally, HiGH and control mice were fed a high-fat diet for 4-weeks, treated with DMBA and monitored during 20-weeks.

Results

The number of AOiGHD females that developed mammary gland tumors was reduced compared to controls, where tumor size and multiplicity were also reduced. Unexpectedly, mammary tumor formation was not increased in chow-fed HiGH mice. In fact, there was a non-significant reduction in tumor multiplicity and a significant delay in tumor latency. Moreover, the number of mice that develop large tumors (>1 cm) was reduced in HiGH mice. In marked contrast, diet-induced obese HiGH mice presented reduced tumor latency and increased tumor incidence, size and multiplicity.

Conclusion

Under normal metabolic conditions (chow-diet), reduced endogenous GH/IGF1 levels in adults protect against mammary gland tumor formation, while elevated endogenous GH/IGF1 levels do not hasten tumor formation. However, under excessive caloric intake, elevated endogenous GH/IGF1 levels accelerate mammary gland tumor formation and progression, indicating the ultimate consequences of excessive caloric intake, elevated endogenous GH/IGF1 levels do not hasten tumor formation. However, under metabolic status in mice.
Objective
To study the anti-tumoral effect of BKM120 and BEZ235, on a model of rat prolactin pituitary tumor SMTW-3.

Methods
One-month after grafted SMTW3 rats were treated via oral gavage 5 days/week with BKM120 (5 mg/kg per day), 20 days; n = 15) or BEZ235 (20 mg/kg per day, 15 days (n=15) or 30 days (n=15)) or control (n=10 for each treatment).

Antitumoral effect was measured by evaluating tumor weight at sacrificed and prolactin plasma level was measured before and after treatment. Ki67 index, mitosis were calculated on tumor section.

Results
BKM120 treatment reduces significantly tumor growth and prolactin secretion compared to controls with a final tumor weight of 4.34 ± 0.27 vs 28.76 ± 7.50 g (P < 0.001) and prolactin concentration of 1909 ± 234.6 vs 5465 ± 1026 µg/l.

BEZ235 treatment was less efficient and reduced tumor growth only after 30 days compared to control (35.87 ± 14.0) vs 47.52 ± 6.9 µg/g; P < 0.05) and did not significantly decrease tumor growth after 15 days (10.89 ± 4.0 vs 11.36 ± 5.8 µg/g) or prolactin secretion after 15 or 30 days of treatment (respectively 6718 ± 3687 vs 7183 ± 4452 µg/l and 6846 ± 3766 vs 8275 ± 4323 µg/l).

Both treatments were associated with a decrease of ki67 index and mitosis compared to tumors in control group.

Conclusion
BKM120, a pure PI3K inhibitor, present promising result for treating patient with aggressive pituitary tumor resistant to any conventional treatment. Differential effect between BKM120 and BEZ2335 on tumor growth and PI3K/akt/tor pathway is under investigation.

DOI: 10.1530/endoabs.32.OC1.4

OC1.6
Management of euvolemic hyponatremia attributed to SIAHD in the hospital: interim results from a prospective, observational, multi-center, global registry
Alessandro Peri1, Joseph Verbalis2, Arthur Greenberg3, Gudmundur Johannsson4, Steven Ball5, Jens Otto Jorgensen6 & Joseph Chiodo III7
1University of Florence, Florence, Italy; 2Georgetown University, Washington, District of Columbia, USA; 3Duke University Medical Center, Durham, North Carolina, USA; 4University of Gothenburg, Gothenburg, Sweden; 5Newcastle University, Newcastle, UK; 6Aarhus University Hospital, Aarhus, Denmark; 7Otsuka America Pharmaceutical, Inc., Princeton, New Jersey, USA.

Introduction
Hyponatremia (HN) is the most common electrolyte disorder of hospitalized patients (pts). It occurs in up to 28% of in-pts, increases in the hospital risk of death by 1.47 fold, and is associated with significantly higher mortality risk following discharge. The HN Registry is the first large scale, international effort to document the clinical characteristics, treatments used, and impact of HN in hospital settings.

Methods
After informed consent or waiver, medical records of pts meeting the registry entry criteria were abstracted. Data are summarized by sample size (n) and percentage (%) for categorical data, and mean±s.d. for continuous data.

Results
One thousand seven hundred and six euvolemic pts with SIAHD enrolled at 157 US and 93 EU sites from Sept 2010 to Dec 2012 had sufficient data for analysis. The mean entry and discharge [Na+] values for pts were 123.1 ± 5.5 and 131.8 ± 4.8 mmol/l. The table summarizes treatments given during hospitalization as treatment episodes of monotherapy (i.e. a treatment that was given alone during a discrete number of days).

Table 1

<table>
<thead>
<tr>
<th>Treatment (Tx)</th>
<th>During hospital stay (%)</th>
<th>Time to Tx from HN (days)</th>
<th>Duration of Tx (days)</th>
<th>[Na+] Correction rate (mmol/l per day)</th>
<th>(Na+) Increase &gt; 12 mmol/l within 24 h of Tx (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment</td>
<td>17% (285)</td>
<td>NA</td>
<td>NA</td>
<td>1.1 ± 1.3</td>
<td>2.0</td>
</tr>
<tr>
<td>Fluid restriction</td>
<td>56% (947)</td>
<td>1.70 ± 0.5</td>
<td>6.64 ± 5.7</td>
<td>1.4 ± 0.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Normal saline</td>
<td>51% (862)</td>
<td>0.75 ± 0.1</td>
<td>2.67 ± 2.4</td>
<td>0.2 ± 0.8</td>
<td>2.0</td>
</tr>
<tr>
<td>Hypertonic saline</td>
<td>12% (212)</td>
<td>1.34 ± 0.1</td>
<td>4.27 ± 1.8</td>
<td>4.2 ± 0.4</td>
<td>11.0</td>
</tr>
<tr>
<td>Tolvaptan</td>
<td>17% (302)</td>
<td>3.44 ± 4.9</td>
<td>5.66 ± 5.0</td>
<td>5.2 ± 6.6</td>
<td>7.0</td>
</tr>
</tbody>
</table>

Conclusions
Fluid Restriction was minimally more effective than no treatment. Tolvaptan and hypertonic saline had the highest correction rates, but the latter was associated with a greater risk of overly rapid correction. More data is needed in this area to inform optimal clinical practice, which will be forthcoming from continuing analysis of the HN Registry.

DOI: 10.1530/endoabs.32.OC1.6

Bone & Calcium

OC2.1
Bone mass accrual following supplementation of vitamin D alone versus vitamin D+ calcium in underprivileged Indian premenarcheal girls
Sunil Kumar Kota1, Lalit Kumar Meher2, Sruti Jannmula2 & Kirtikumar D Modi2
1Medwin Hospital, Hyderabad, Andhra Pradesh, India; 2MCG Medical College, Berhampur, Orissa, India; 3Roland Institute of Pharmaceutical Sciences, Berhampur, Orissa, India.

Objective
To determine effectiveness of supplementing vitamin D alone vs vitamin D+ calcium on bone mass accrual in underprivileged Indian premenarcheal girls.

Methods
A double blind, matched pair, cluster randomization study was carried out in 200 premenarcheal girls (8–12 years) from three public schools. The participants were randomized into two clusters and were allocated to receive either vitamin D (Group A): 30 000 IU oral cholecalciferol every 3 months or vitamin D + calcium (Group B): 500 mg/day calcium and vitamin D 30 000 IU oral cholecalciferol every 3 months. The supplementation trial was done for the duration of 1 year. Anthropometry, biochemical parameters, total body bone area (TBB), mineral content (TBBMC) and bone mineral density (TBBMD) by dual energy X-ray
absorption were assessed at baseline and at the end of 1 year.

Results
At baseline vitamin D deficiency was observed in 84 (42%) girls. Post supplementation TBBMC, TBBMD and TBBA were significantly increased in both the groups in comparison to baseline. But the corresponding Z scores showed significant improvement only in group B. Mean percent increase in TBBMC was significantly higher in group B (from 84 ± 174 to 1018 ± 226 g, 22.3%) compared to group A (from 793 ± 138 to 935 ± 185 g, 17.6%, P = 0.02).

Improvement in TBBMC-for-age Z score was higher in the group B (from -1.1 ± 0.9 to -0.9 ± 0.2, 22%) vs group A (from -1.1 ± 0.7 to -1.1 ± 0.8, 13.6%, P = 0.03). Similarly increments in TBBMD were significantly higher in group B (from 0.78 ± 0.05 to 0.82 ± 0.06 g/cm², 5.5%) vs group A (from 0.77 ± 0.05 to 0.80 ± 0.05 g/cm², 3.3%, P = 0.03). However increase in TBBA was not significantly different between the two groups (14.4% in group B vs 13.8% in group A, P > 0.1).

No significant difference in mean percent increase in TBBMC were observed across vitamin D categories (< 20, 20–30, > 30 ng/ml) in both the groups. The increase in height was similar in the two supplemented groups (7.3 ± 1.5 cm in group A vs 7.4 ± 1.4 cm in group B).

Discussion
Low adult bone mass is linked to osteoporosis and fractures and is dependent on the extent of childhood and adolescent bone mineralization. Indices of bone health improved significantly following calcium and vitamin D supplementation.

Conclusion
Calcium along with vitamin D supplementation was more effective in improving bone mass accrual in underprivileged premenarcheal girls than vitamin D alone.

DOI: 10.1530/endoabs.32.OC2.1

OC2.2
Influence of vitamin D and calcium on reproductive hormones: a study in a VDR-ablated male mouse model and 300 healthy men
Martin Blomberg Jensen, Liesbet Lieben, John E Nielsen, Ariane Willems, Anders Juul, Niels Jørgensen, Jorma Toppari, Geert Carmona Beek and Emanuele Ferrante

Introduction
Vitamin D (VD) is metabolized locally in the tissues, and ablation of the VD receptor (Vdr) in mice has proven a valid model for hereditary VD resistant rickets. However, only one of three published Vdr−/− strains presented with male infertility. Here, we investigated reproductive hormones, gene expression and the testicular histological phenotype of male Vdr−/− mice, and associated these results with reproductive hormone levels of men with different VD status.

Material and methods
In total 9 wildtype Vdr+/−, 8 Vdr−/−, and 11 Vdr+/+ mice were investigated at the age of 10 and 15 weeks. Histology and gene-expression were examined in murine testis tissue by q-PCR and immunohistochemistry. Murine serum gonadotropins, testosterone and estradiol were measured with immunoassays. Serum levels of 25-hydroxyVD and calcium were subsequently established in a cross-sectional study of 300 men from the general population and associated with serum concentrations of estradiol, testosterone, Inhibin B, SHBG, LH and FSH.

Results
Testicular histology was grossly normal in Vdr−/− mice without differences in tubular diameter, epithelial width or Leydig cell-numbers. No changes were found in serum hormone levels and accordingly, no difference in expression of Cyp19α1a, Erα, 17ß-hsd, Star, Inhibin B, and Anh. However, a significantly lower expression of Erβ in testis and epididymis (P < 0.05) was found in Vdr−/− and Vdr+/−. In the human study, 44% were VD insufficient (<50 nM), and 25-hydroxyVD correlated positively with SHBG and negatively with free androgen index (FAI) (P < 0.05), while albumin-corrected calcium had the opposite effect. Adjusted regression analyses confirmed the associations of VD and calcium with SHBG and FAI (P < 0.05).

Conclusion
VD is apparently dispensable for testicular hormone biosynthesis in mice and humans, but may be regulating Erβ expression in murine testis and epididymis. The associations between serum 25-hydroxyVD and calcium with SHBG/FAI in men indicate a systemic rather than testicular effect of VD.

DOI: 10.1530/endoabs.32.OC2.2

OC2.3
Screening for GNAS genetic and epigenetic alterations in progressive osseous heteroplasia: first Italian series
Francesca Marta Elli, Annamaria Barbieri, Paolo Bordogna, Elena Giardino, Emanuele Ferrante, Paolo Beck-Peccoz, Anna Spada & Giovanna Mantovani

Endocrinology and Diabetology Unit, Department of Clinical Sciences and Community Health, University of Milan, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy.

Progressive osseous heteroplasia (POH) is a rare autosomal dominant disorder of mesenchymal differentiation characterized by progressive heterotropic ossification (HO) of dermis, skeletal muscle and deep connective tissues. Initially HO occurs during infancy as osteoma cutis, then extends progressively into deep connective tissues during childhood. Most cases of POH are caused by paternally inherited mutations of GNAS gene. Maternal mutations as well as epigenetic defects of the same gene lead to pseudohypoparathyroidism (PHP) and Albright’s hereditary osteodystrophy (AHO). Recently, some reports documented the existence of POH patients showing additional features characteristics of PHP/AHO. Thus, POH has been proposed to be part of the spectrum of HO disorders caused by inactivating GNAS mutations.

We investigated nine unrelated POH patients, one of whom also showed resistance to PTH and TSH, for GNAS genetic and epigenetic status by direct sequencing and MS-MLPA. In a subset of patients, we performed RNA seggregation analysis in order to establish the parental origin of the mutated allele.

We detected Four GNAS mutations in five of nine patients, all de novo and predicting truncated proteins. In three mutated patients, we demonstrated that the mutation occurred on the paternal allele. No evident differences were observed among patients harboring different mutations, as well as between mutated and non-mutated patients. Thus, neither the presence/absence nor the type or the localization of the mutation allowed to predict a specific phenotype or the severity of progression within the spectrum of GNAS-related disorders. All tested POH patients resulted wild type for GNAS imprinting status and no copy number abnormalities were found.

In conclusion, our results support that POH belongs to a continuum of HO disorders associated with inactivating GNAS mutations and further expand the spectrum of associated genetic defects. Moreover, unlike PHP, methylation alterations at GNAS locus are absent or uncommon in POH.

DOI: 10.1530/endoabs.32.OC2.3

OC2.4
Natural course of changes in bone mineral density after orthotopic liver transplantation: up to 5 years follow-up in a single centre
Charlotte Krol, Ola Dekkers, Deni Meiland, Bart van Hoes & Neven Hamdy

Leiden University Medical Centre, Leiden, The Netherlands.

Introduction
Low energy trauma fractures are prevalent in end-stage liver disease and after orthotopic liver transplantation (OLT). However, data on bone mineral density (BMD) are scarce in these patients. In this study, we evaluated the natural course of changes in BMD after successful OLT.

Study design
All recipients of a successful OLT between 2000 and 2011 from the Leiden University Medical Centre, in whom BMD data were available, were included. Patients treated with bisphosphonates were censored at start of bisphosphonate therapy (last observation carried forward). Follow-up duration was five years.

Results
The cohort consisted of 223 patients, 69% men, mean age of 50 (17–70 years). Most common primary liver pathology was viral (31%) or alcoholic liver disease (23%). All patients received prednisone, the majority either tacrolimus or cyclosporine. At screening, osteoporosis or osteopenia were found in 18 and 38% of patients at the lumbar spine (LS) and in 10 and 45% of patients at the femoral neck (FN). BMD declined significantly at both sites 6 months after OLT, but increased thereafter at the LS, reaching pre-transplant values at 2 years, and subsequently stabilizing. In contrast, FN BMD declined from 6 months onward, remaining consistently lower than pre-transplant values. The cumulative incidence of osteoporosis at five years after OLT was 14.6% at the LS and 19.6% at the FN.

Conclusion
Osteoporosis and osteopenia are prevalent in patients with end-stage liver disease. An overall decline in BMD is observed within the first 6 months after OLT, with subsequent recovery to pre-transplant values at the LS, but with further decline at the FN. Further investigations are currently underway to elucidate the potential
factors responsible for bone loss before and after OLT and to examine the predictive value of changes in BMD for risk of fracture in these patients.

DOI: 10.1530/endoabs.32.OC2.4

OC2.5

Genetic analysis of CDKN1B gene in familial primary hyperparathyroidism
Elena Pardi1, Simonna Borsari1, Federica Saponaro1, Chiara Banti1, Natalia Pellegrata2, Misia Lee3, Edda Vignali1, Antonella Meola1, Katia Jedeon1,2, Muriel Molla De La Dure 2,3, Steven Brookes4, Marco Mastinu1, Stefano Mariotti2, Claudio Marcocci1 & Filomena Cetani1

1Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; 2Endocrinology Unit, Department of Medical Sciences, Policlinico di Monserrato, University of Cagliari, Cagliari, Italy; 3Institute of Pathology, Helmholtz Zentrum München-German Research Center for Environmental Health, Neuherberg, Germany.

Primary hyperparathyroidism (PHPT) is usually a sporadic disorder, but in <10% of cases occurs as part of hereditary syndromes, including multiple endocrine neoplasia types 1 and 2A (MEN1 and MEN2A), hyperparathyroidism-jaw tumor syndrome (HPT-JT) and familial isolated hyperparathyroidism (FIHP). MEN 1 is an autosomal dominant disorder characterized by tumours in multiple endocrine glands, most commonly parathyroid, enteropancreatic and anterior pituitary glands. To date, germline mutations in the MEN1 gene have been identified in 70-80% of MEN1 kindreds. FIHP has a heterogeneous molecular etiology, since germline mutations in MEN1, HRPT2 and CASR genes have been reported. Recently, germline mutations of cyclin dependent kinase inhibitor 1B (CDKN1B) gene, encoding the p27 protein, have been identified in 8 kindreds with MEN1 syndrome which were negative to the MEN1 genetic screening.

The aim of this study was to perform a genetic screening of CDKN1B gene in patients with MEN1 syndrome and FIHP (33 and 17, respectively). All MEN1 and FIHP probands were negative for MEN1 gene mutations at genetic testing. Genomic DNA from index cases was analyzed by PCR amplification of the entire coding region and splice sites, and direct sequencing was performed by a 16-capillaries automated sequencer.

A novel frameshift germline mutation in CDKN1B gene, c.372_373delCT/p. Asn124AsfsX2, was identified in a MEN1 proband. A construct expressing p27_c.372_373delCT was generated to assess the functional properties of the mutant protein in vitro. Indirect immunofluorescence demonstrated that the mutant protein is mainly retained in the cytoplasm, affecting the cell cycle inhibitory function of p27 in the nucleus. Our results confirm that germline CDKN1B mutations are involved, although rarely, in parathyroid tumorigenesis.

DOI: 10.1530/endoabs.32.OC2.5

OC2.6

Hypomineralized teeth as biomarkers of exposure to endocrine disruptors
Katja Jedeon1,2, Muriel Molla De La Dure2,3, Steven Brookes4, Clemence Mercano1, Marie-Chantal Canivenc-Lavier1, Ariane Berdal1,2 & Sylvie Babajko3

1INSERM UMR5 872, Laboratory of Molecular Oral Pathophysiology, Paris, France; 2Université Paris-Diderot, UFR d’Odontologie, Paris, France; 3Reference Centre for Rare Malformations of the Face and Oral Cavity, Hospital Rothschild, Paris, France; 4Department of Oral Biology, Leeds Dental Institute, Leeds, UK; 5INRA UMR 1324, Université de Bourgogne, Dijon, France.

MIH for Molar Incisor Hypomineralization is a recently described pathology affecting around 18% of six year old children. Although a number of putative factors have been hypothesized, etiology of MIH remains unknown. The parallel increase of exposure to endocrine disruptors (EDs) and the prevalence of MIH led us to investigate a possible relationship between both events.

Rats were orally exposed daily to low dose of bisphenol A (BPA), genistein, vinclozolin, alone (for BPA) or in combination, from the conception to the sacrifice, mimicking human environmental exposure. Macroscopic observation of male rat incisors showed that the phenotype induced by BPA was the most evident with 75% of rats presenting random opaque white spots comparable to those observed in human MIH, whereas only 50% of GEN and VINCLO treated rats showed similar phenotype. Human MIH and BPA treated rat teeth were analyzed in parallel by scanning electron microscopy (SEM) - Energy dispersive X-ray (EDX) and histology. Both of them exhibited the same hypomineralization phenotype. BPA targeted specifically the expression of the two major enamel genes, enamelin and kallikrein 4 (Klk4) at the transcriptional level. Rat ameloblastic HAT-7 cells were stably transfected with plasmids containing KLK4 promoter, and treated with 1 nM BPA, 1 nM GEN, 1 nM VINCLO. BPA decreased both KLK4 mRNA level and KLK4 promoter activity. Conversely, GEN increased KLK4 expression whereas VINCLO had no effect on this gene, a possible reason for the lesser effect on enamel hypomineralization.

Our data strongly support a role for EDs acting as BPA in MIH pathology. In conclusion, MIH teeth may represent a much needed early biomarker, easily accessible, for ED exposure in humans.

DOI: 10.1530/endoabs.32.OC2.6

Thyroid

OC3.1

Targeting of PATZ1 by miR-29b is a downstream effect of oncogenic Ras signalling in thyroid cells
Michela Vitello1,2, Teresa Valentinò1,2, Marta De Menna3, Lucia Serpico1, Sonia Matsueto1, Gabriella De Vita1, Alfredo Fusco1,2 & Monica Fedele1

1Istituto di Endocrinologia ed Oncologia Sperimentale del CNR, Naples, Italy; 2Dipartimento di Biologia e Patologia Cellulare e Molecolare, Università degli Studi di Napoli ‘Federico II’, Naples, Italy.

PATZ1, a member of the POZ-ZF protein family of transcription factors is emerging as an important cancer-associated factor that can act either as oncogene or tumour-suppressor depending on the cellular context. Consistent with a tumour-suppressor role in thyroid cells, we have shown that PATZ1 is highly downregulated in anaplastic thyroid carcinomas compared to normal thyroid tissue and is a powerful inhibitor of anaplastic thyroid cancer cell survival, migration, invasiveness and tumorigenicity.

Looking for the upstream signalling pathway regulating PATZ1 expression in thyroid cells, we searched for microRNAs targeting PATZ1. In order to identify miRNAs predicted to bind the 3’UTR of PATZ1 we used bioinformatics free tools, based on the miRanda application and the mirSVR predicted target site scoring method. Among the miRNAs identified by this analysis we validated miR-29b. Indeed, we demonstrated that it is able to target PATZ1 and cause downregulation of PATZ1 expression at both mRNA and protein level in different cell systems, including rat thyroid cells. Interestingly, miR-29b is induced by Ras during transformation of FRTL-5 rat thyroid cells toward an undifferentiated phenotype, resembling that of anaplastic carcinomas and characterized by the acquisition of a migratory and invasive behaviour. In these cells, we observed a strong down-regulation of PATZ1 expression, which starts as early as 2 h after Ras induction, and an inverse correlation between the expression of miR-29b and PATZ1 mRNA and protein levels.

These results are consistent with the suppressor role of PATZ in thyroid carcinogenesis and suggest that down-regulation of PATZ1 expression, through miR-29b, may be a downstream effect of the oncogenic Ras signalling in thyroid cell transformation.

DOI: 10.1530/endoabs.32.OC3.1

OC3.2

Mitochondrial mass and function is regulated by PI3K signaling in thyroid cancer cells
K Alexander Iwen, Erich Schröder, Julia Resch, Ulrich Lindner, Peter König, Hendrik Lehnert, Nina Perwitz, Saleh Ibrahim & Geir Brabant

Universität zu Lübeck, Lübeck, Germany.

Objective

Abnormal mitochondria are well known in oxyphilic thyroid tumors but recent data also confirm profound mitochondrial alterations in other thyroid carcinomas. These changes are linked to the aggressiveness of the tumors. Our group recently demonstrated in an in vivo model, that inhibition of phosphoinositide 3-kinase (PI3K) signalling suppressed the invasive and metastatic behaviour of thyroid cancer cells. Here, we evaluated whether a modulation of PI3K signalling changes mitochondrial mass and function.

Methods

We used follicular (FTC-133, WRO) and anaplastic (8505C) carcinoma cell lines, including rat thyroid cells. Interestingly, miR-29b is induced by Ras during transformation of FRTL-5 rat thyroid cells toward an undifferentiated phenotype, resembling that of anaplastic carcinomas and characterized by the acquisition of a migratory and invasive behaviour. In these cells, we observed a strong down-regulation of PATZ1 expression, which starts as early as 2 h after Ras induction, and an inverse correlation between the expression of miR-29b and PATZ1 mRNA and protein levels.

These results are consistent with the suppressor role of PATZ in thyroid carcinogenesis and suggest that down-regulation of PATZ1 expression, through miR-29b, may be a downstream effect of the oncogenic Ras signalling in thyroid cell transformation.

DOI: 10.1530/endoabs.32.OC3.1

Endocrine Abstracts (2013) Vol 32
Results
Mitochondrial mass remained unchanged in all cell lines but active mitochondria were significantly decreased by acute PI3K inhibition. This effect was most pronounced in FTC-133 cells. It was accompanied by a significant shift in oxygen consumption (directly measured by Clarke electrode), a decrease in the production of reactive oxygen species (Dihydorhodamine 123 and MitoSOX) and reduced protein carbonylation (OxyBlot). Evaluation of proteins involved in mitochondrial biogenesis (PGC1α) and mitochondrial autophagy (BNIP3 and Beclin1) indicate a shift in the balance of biogenesis and autophagy upon acute PI3K inhibition. Electron microscopy confirmed a major change in mitochondrial ultrastructure and an increased number of lysosomes/autophagosomes.

Summary
Our data demonstrate that changes in PI3K signaling alter mitochondrial function. These functional data suggest a major impact of the PI3K cascade on the reprogramming of mitochondria in cancer. These mitochondrial alterations may have important consequences to explain the aggressiveness of thyroid cancer subtypes with activated PI3K.

DOI: 10.1530/endoabs.32.OC3.2

OC3.3 – ESE Young Investigator Award
SP600125, a new p53 selective anticancer drug: effects on poorly differentiated thyroid cancers
Elisa Stellaria Grassi1, Valeria Vezzoli1, Irene Negri2 & Luca Persani1-4
1Università degli Studi di Milano, Dipartimento di Scienze Cliniche e di Comunità, Milano, Italy; 2Istituto Auxologico Italiano, IRCCS, Laboratory of Endocrine and Metabolic Research, Milan, Italy; 3Università degli Studi di Milano, Milano, Italy; 4Istituto Auxologico Italiano, IRCCS, Division of Endocrine and Metabolic Diseases, Milan, Italy.

Poorly differentiated thyroid cancers are associated with variable types of p53 function derangements and bad prognosis due to the lack of effective treatments. SP600125 is a widely used JNK inhibitor which recently showed anticancer properties in a p53 related way. Here, we tested the effect of SP600125 on four different thyroid cancer cell lines derived from PDTCs and ATCs with different p53 status.

We analyzed the effects on cellular replication and apoptosis, changes in morphology or intracellular pathway activities. Our results show that SP600125 is able to suppress the growth of the three p53-mutated cell lines but not of the p53-null one with significant results after 48 h of incubation and EC50 of 1.3–8.4 μM. This effect is accompanied by a slight caspase 3 activation confirmed by functional assay and western-blotting.

The growth inhibition is correlated with an increase of p21 expression levels of more than 3-fold and a 2-fold increase in nuclear dimensions, thus consistent with significant effects on cell cycle progression and DNA accumulation.

Moreover, we observe that SP600125 treatment in the p53-mutated cells causes polymerized tubulin stabilization, as shown by the relative increase of polymer versus monomer form; this is accompanied by increased polymerized tubulin acetylation, a marker of microtubules stability. Confocal microscopy showed morphological alteration of treated cells as well as differences in acetylated tubulin distribution, with a switch from physiological perinuclear organization to cytoplasmatic distribution. These alterations correlate with an increase of cytoplasmic and nuclear area, with variations in p53 and JNK subcellular localization.

All together these data confirm that SP600125 acts in a p53-dependent way and it’s able to induce cell growth arrest with significant effects on nuclear and cell division, microtubule organization and intracellular protein distribution in a subgroup PDTC cells. SP600125 appears a reliable candidate drug for PDTCs harbouring p53 mutations.

DOI: 10.1530/endoabs.32.OC3.3

OC3.4 DNA methylation signatures identify biologically distinct thyroid cancer subtypes
Juan Luis Fernandez-Morera1,2, Sandra Rodriguez-Rodero2, Elias Delgado Alvarez1, Agustin Fernandez-Fernandez2, Ivan Fernandez-Vega4, Rocío González-Marqués1, Verónica Sanchez-Rivas1, Lorena Suárez-Gutierrez2, Maria Galiana Rodriguez Caballero1, Jessica Ares Blanco1, Mario Fernandez-Fraga1 & Edelmiro Menendez-Torre2
1Endocrinology and Nutrition Service, Hospital Universitario Central de Asturias, Oviedo, Asturias, Spain; 2Cancer Epigenetics Laboratory, Instituto Universitario de Oncología del Principado de Asturias (IUOFA), Universidad de Oviedo, Oviedo, Asturias, Spain; 3Otolaryngology Service, Hospital Universitario Central de Asturias, Oviedo, Asturias, Spain; 4Pathology Service, Hospital Universitario Central de Asturias, Oviedo, Asturias, Spain.

Introduction
The global patterns of aberrant DNA methylation in thyroid cancer are not known. In this study, we have used DNA methylation arrays to determine, for the first time, the genome-wide promoter methylation status of different subtypes of thyroid tumors.

Material and methods
We analyzed a cohort of 54 snap frozen thyroid samples (thirteen papillary tumors, six follicular, eleven anaplastic, twenty medullar and four normal tissue samples). Also human thyroid carcinoma-derived cell lines, K1, FTC-133, 8305C and TT were obtained from the ECACC to analyze. A microarray-based DNA methylation profiling was performed with the Illumina Infinium Human Methylation 27K Platform with some of these samples. Hierarchical cluster analysis and definition of differentially methylated genes, computational gene expression analysis and gene ontology analysis of differentially methylated genes were performed. To confirm those data, bisulfite pyrosequencing of several genes were also done. Also proportions of PcG-marks and bivalent domains in different methylation groups were studied.

Results
We identified 262 and 352 hyper and 13 and 21 hypomethylated genes in differentiated papillary and follicular tumors respectively. Surprisingly, undifferentiated tumors displayed more hypomethylated genes (280 in anaplastic, 393 in medullar) than aberrantly hypermethylated genes (86 in anaplastic, 131 in medullar). Hypermethylated genes in tumors originating from follicular cells were preferentially involved in developmental processes whilst those in medullary tumors were primarily involved in cell signaling and iodine pathways.

Hypomethylated genes were involved in immune system functions. Among the genes identified, we show that four potential tumor suppressor genes (ADAMTS5, HOXB4, ZIC1, and KISS1R) and four potential oncogenes (NISL4, DPPA2, TCG1, and NOTCH4) are frequently regulated by aberrant methylation in thyroid tumors.

Further studies are needed to determine the potential clinical interest of the subtype-specific DNA methylation signatures described herein and the role of aberrant promoter hypomethylation in undifferentiated thyroid tumors.

DOI: 10.1530/endoabs.32.OC3.4

OC3.5 Role of the calcium-calmodulin dependent kinase 2 in medullary thyroid carcinoma
Eleonora Russo1, Marcella Salzano1, Valentina De Falco1, Massimo Santoro2, Caterina Mian2, Susi Barollo2 & Mario Vitale3
1University of Naples Federico II, Naples, Italy; 2University of Padua, Padua, Italy; 3University of Salerno, Baronissi, Salerno, Italy.

Recent studies demonstrated that the calcium/calmodulin dependent kinase 2 (CaMKII) is involved in the regulation of proliferation and survival of epithelial cells, were it phosphorylates RAP1 and modulates MAPK pathway. A endogenous CaMKII inhibitor (hCaKINtα) is expressed in some cell types. It is down-expressed in colon and in ovarian cancer where it inversely correlates with the disease extension.

Aim of our study is to determine the possible role of CaMKII in the medullary thyroid carcinoma (MTC), to determine whether hCaKINtα is expressed, and whether its level of expression correlates with the clinicopathological features of MTC.

To this purpose, RETC634Y e RETM918T, two RET mutants most frequently found in MTC cell lines were it mediates the oncogenic pathway leading to cell proliferation. These alterations correlate with an increase of ERK phosphorylation and cell proliferation. The expression of hCaKINtα RNA expression.

Gender and age at diagnosis did not correlate with hCaKINtα RNA expression. Z volume (P=0.0094 by ANOVA), lymph node metastasis (P=0.0297 by t-test) and staging (P=0.0043 by ANOVA) were negatively correlated with the expression of hCaKINtα mRNA.

In conclusion, CaMKII is activated by RET mutants and is activated at baseline in MTC cell lines. hCaKINtα is expressed, and its level of expression correlates with the clinicopathological features of MTC.

To this purpose, RETC634Y e RETM918T, two RET mutants most frequently found in MTC, were it mediates the oncogenic pathway leading to cell proliferation. Then, the expression of hCaKINtα RNA was determined by real-time PCR in 24 primary MTCs and was correlated with some clinicopathological parameters. Gender and age at diagnosis did not correlate with hCaKINtα RNA expression. Z volume (P=0.0094 by ANOVA), lymph node metastasis (P=0.0297 by t-test) and staging (P=0.0043 by ANOVA) were negatively correlated with the expression of hCaKINtα mRNA.

In conclusion, CaMKII is activated by RET mutants and is activated at baseline in MTC cell lines. hCaKINtα is expressed, and its level of expression correlates with the clinicopathological features of MTC.
OC3.6 – ESE Young Investigator Award
Subclinical hyperthyroidism and risk of cardiovascular and all-cause mortality

Christian Selmer1, Jonas Olesen1, Jesper Madsen2, Jens Faber3, Peter Hansen1, Ole Pedersen1, Morten Hansen1, Christian Torg-Pedersen4 & Gunnar Gislason1
1Department of Cardiology, Gentofte University Hospital, Hellerup, Denmark; 2Department of Endocrinology, Herlev University Hospital, Herlev, Denmark; 3Department of Cardiology, Roskilde University Hospital, Roskilde, Denmark; 4Department of Cardiology, Herlev University Hospital, Herlev, Denmark; 6Institute of Health, Science and Technology, Aalborg University, Aalborg, Denmark.

Background
It is still discussed if subclinical hyperthyroidism and ‘high-normal’ thyroid function are risk-factors for cardiovascular mortality.

Objectives
To examine the risk of cardiovascular and all-cause mortality in relation to subclinical hyperthyroidism.

Methods
Patients consulting their general practitioner from 2000 to 2009 in Copenhagen, Denmark, who underwent thyroid blood tests, were identified by individual-level linkage of nationwide registers. Patients with a history of thyroid disease or related medication were excluded. Risk of cardiovascular mortality was analyzed using Kaplan-Meier curves and Poisson regression models were applied to estimate Incidence Rate Ratios (IRR).

Results
Of 574 995 included individuals (mean age 48.7 years (s.d. ±18.3); 39.1% males) 550 927 (95.9%) were euthyroid, 1603 (0.3%) had overt hypothyroidism, 11 834 (2.1%) subclinical hypothyroidism, 3967 (0.7%) overt hyperthyroidism and 6264 (1.1%) subclinical hyperthyroidism. Increased risk of cardiovascular mortality was found in two levels of subclinical hyperthyroidism (TSH <0.1, 0.1–0.2 mU/l and normal free thyroxine): IRR 1.24 (95% CI: 1.09–1.41), IRR 1.21 (1.09–1.34) and in ‘high-normal’ levels of euthyroidism (TSH 0.2–0.4 mU/l): IRR 1.24 (95% CI: 1.09–1.41), IRR 1.21 (1.13–1.29).

Conclusions
Subclinical hyperthyroidism and ‘high-normal’ thyroid function are significant risk-factors for cardiovascular and all-cause mortality.

DOI: 10.1530/endoabs.32.OC3.6

OC4.1
Pre-clinical model detects castrate-resistant cancer repopulating cells in localised prostate tumours

Gail Risbridge1, Roxamne Toivanen1, Mark Frydenberg1, Declan Murphy2, John Pedersen1, Andrew Ryan1, David Pook1, David Berman1 & Renea Taylor1
1Monash University, Melbourne, Victoria, Australia; 2Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; 3TissuPath Laboratories, Melbourne, Victoria, Australia; 4Queen’s University, Kingston, Ontario, Canada.

Introduction
Lack of clinically relevant experimental models of human prostate cancer hampers evaluation of novel therapeutic agents. Currently, androgen deprivation therapy is the gold standard treatment for advanced prostate cancer, but inevitably cells survive and repopulate the tumour. Castrate-resistant cells are critical therapeutic targets for more effective treatments but current model systems cannot determine when they arise in disease progression and are unable to recapitulate variable patient response to treatment.

The aim of this study was to develop stromally supported xenografts from multiple patients with early stage-localised disease to investigate the castration response. It was postulated that prior to the development of aggressive/metastatic disease, localised prostate cancer specimens may already harbour castrate-resistant, cancer repopulating cells.

Methods
To test this concept a reproducible and reliable model was used to establish 12 patient localised prostate cancers in vivo. Using these 12 engrafted tumours, response to short and long term castration, as well as androgen restoration was examined. Tumour grafts were analysed using pathology, proliferation/apoptotic indices and biomarker expression.

Results
Histopathology of all 12 engrafted tumours mimicked that of the original tumours and when host mice were castrated, the tumours regressed showing significant changes in proliferation and apoptosis. Four weeks thereafter, a population of growth quiescent luminal cells, expressing low AR and PSA remained. These cells survive and repopulate the tumour. Castrate-resistant cells are critical therapeutic targets for more effective treatments but current model systems cannot determine when they arise in disease progression and are unable to recapitulate variable patient response to treatment.

Conclusions
Stem-like castrate-resistant (but hormone sensitive) tumour cells were detected in localised prostate cancer specimens from which tumours regenerate, thus proving the need to further characterise these cells and elucidate common pathways to therapeutically target them.

DOI: 10.1530/endoabs.32.OC4.1

OC4.2
Single nucleotide polymorphism array profiling of adrenocortical tumors: evidence for an adenoma carcinoma sequence?

Cristina Ronchi1, Silvia Sbiera1, Ellen Leich1, Andreas Rosenwald2, Bruno Alloio1 & Martin Fassnacht1,3
1Unit of Endocrinology and Diabetes, University Hospital, Wuerzburg, Germany; 2Department of Pathology, University of Wuerzburg, Wuerzburg, Germany; 3Department of Internal Medicine IV, University Hospital Munich, Munich, Germany.

Background
Adrenocortical tumors consist of benign adenomas (ACA) and highly malignant carcinomas (ACC) with a still incompletely understood pathogenesis. Our aim was to test, whether there is evidence for an adenoma-carcinoma sequence.

Methods
High-resolution single nucleotide polymorphism (SNP) microarrays (Affymetrix SNP 6.0) were used to detect copy number alterations (CNAs) and copy neutral losses of heterozygosity (cnLOH) in 46 adrenocortical tumors (24 ACA and 22 ACC) matched with normal samples.

Results
Genomic clustering showed good separation between ACA and ACC samples, with the best partition for chromosome (chr) 5, which was highly amplified in 17/22 ACC. Of note, the median number of CNA per tumor was not significantly different between ACA and ACC (43.5 vs 132; P = n.s.). However, recurrent CNAs (observed in >2 samples, frequency >15%), the median number of large CNAs (>100 Kb) or CN losses, and the percentage of samples affected by cnLOH were significantly higher in ACC (3993 vs 98 recurrent CNAs; 62.5 vs 7 large CNA; 72.5 vs 5.5 CN losses; 90.9 vs 29.1% cases with cnLOH, P 4% for each). Interestingly, more than 70% of alterations found in ACA were also present in ACC, most of them being observed in chr 5p15.33, 9q32–34, 16p13.3, and 19p13.3 and involving among others 11 growth factors, 41 transcription factors, 16 protein kinases, and 11 oncogenes. In addition, Notch signaling was the most frequently altered pathway in both tumor entities. Finally, a CN gain at chr 11p15.5 (“IGF2 locus”) appears to be an early alteration in a multi-step tumor progression (present in 25% of ACA), followed by loss of one allele leading as a second hit to a cnLOH with consecutively increased expression of the imprinted IGF2 gene only in malignant adrenal tumors.

Conclusions
Our results on genetic alterations support the concept of an adenoma-carcinoma sequence in adrenocortical carcinoma.

DOI: 10.1530/endoabs.32.OC4.2

Endocrine Abstracts (2013) Vol 32
OC4.3
Prognostic factors of advanced unresectable by stage III and IV ENS@T adrenocortical carcinomas (ACC)
Rossella Libe1, Isabelle Borget1, Cristina Konchi1, Massimo Terzolo1, Michaela Haaf2, Federica Laino3, Thomas Kherkhof2, Elisa Corsini2, Antoine Tabarin1, Olivier Chabo3, Christelle De la Fouchardiere4, Patricia Niccoli10, Philippe Caron1, Massimo Mannelli5, Harm Haak3, Felix Beuchlein1, Jerome Bertherat13, Alfredo Berruti1, Martin Fassnacht3 & Eric Baudin2
1National Network COMETE, Paris, France; 2Institute Gustave Roussy, Villejuif, France; 3University of Wuerzburg, Wuerzburg, Germany; 4University of Orbassano, Orbassano, Italy; 5University of Einthoven, Einthoven, The Netherlands; 6University of Florece, Florence, Italy; 7CHU Bordeaux, Bordeaux, France; 8CHU Grenoble, Grenoble, France; 9Centre Léon Berard, Lyon, France; 10CHU Marseille, Marseille, France; 11CHU Toulouse, Toulouse, France; 12University of Munich, Munich, Germany; 13Université Paris Descartes, Paris, France; 14University of Brescia, Brescia, Italy.

Introduction
The prognosis of stages III–IV ACC patients is dismal. The 5-year survival of stage IV ACC ranges between 0 and 13% and no prognostic study has focused on stage III, yet. Several reports suggest a greater heterogeneity of advanced ACC prognosis that initially thought.

Aim
The primary objective of our study was to analyse the prognostic factors of overall survival of the subgroup of advanced unresectable stage III–IV ACC patients collected in the ACC-ENS@T registry.

Methodology
The primary end-point was to determine the median overall survival (OS). Secondary objectives were: 1) 5-year OS, to refine the prognostic stratification, to analyse the role of early ACC management and delays in treatment. All relevant clinical parameters as well as therapeutic management were captured. Weiss score and ki67 index performed in a subgroup of patients (236 and 122, respectively) were analyzed in a second model.

Patients and methods
Three hundred and thirty-four adult patients were enrolled (100 stage III and 234 stage IV ACC) treated between 2000 and 2009. Inclusion criteria were: age > 18 years, unresectable ACC (R1, R2, Rx), clinical and follow-up data available.

Results
After a median follow-up of 60 months two hundred and fifty patients (74%) died. Median OS was 20 months. The 1-, 2-, and 5-years survival rates were 67, 42 and 19%, respectively.

At multivariate analysis, age >50 years (HR = 1.4, P = 0.02), glucocorticoids secretion (HR = 1.3, P = 0.04), number of tumor organs > 3 (HR = 3.2, P < 0.0001), adipsé infiltration (HR = 1.8, P = 0.0099) and adrenallectomy (HR = 0.4, P < 0.0001) were significantly associated with the risk of death. When pathological parameters were entered in the MV model, only Ki-67 > 20% HR = 3.6, P = 0.001) remained significant.

Conclusion
This large ENSAT prognostic study allows to propose a prognostic stratification of advanced ACC patients that will drive future therapeutic approaches. Surgery of adrenal primary is confirmed as a major therapeutic intervention. Ki 67 determination becomes mandatory.

DOi: 10.1530/endoabs.32.OC4.3

OC4.4
Neuronal dysfunction in the hippocampi of cured Cushing’s syndrome patients, detected by HI-MRS-spectroscopy
Eugenia Resmini1, Alicia Santos1, Beatriz Gómez-Anson2, Olga López-Morelo3, Patricia Pires3, Yolanda Vives-Gilabert2
1Endocrinology/Medicine Departments, Hospital Sant Pau, Centro de Investigacion Biomedica en Red de Enfermedades Raras (CIBER-ER, Unidad 747), IIB-Sant Pau, ISCIII and Universitat Autònoma de Barcelona, Barcelona, Spain; 2Neuroradiology Unit, Hospital Sant Pau, and IIB-Sant Pau, UAB, Barcelona, Spain; 3Port d’Informació Científica (PIC) and Institut de Física d’Altes Energies (IFAE), Campus UAB Edifici D, Bellaterra, Barcelona, Spain; 4Department of Psychiatry, Hospital Sant Pau, UAB, Barcelona, Spain.

Introduction
Proton magnetic resonance spectroscopy (1H-MRS) is a sensitive, non-invasive imaging technique capable of measuring brain metabolites in vivo. Chronic exposure to endogenous hypercortisolism in Cushing’s syndrome (CS) is associated with negative effects on memory and hippocampal volumes, even after biochemical cure.

Objective
To investigate metabolites in the hippocampi of CS patients and controls, using 1H-MRS.

Patients and methods
EIGHTEEN right-handed cured CS patients (age 44.8 ± 12.5 years, 12.6 ± 3.8 years of education), 18 right-handed healthy controls, matched for age (40.0 ± 11.9 years) and years of education (14.4 ± 3.8) underwent 3-Tesla magnetic resonance imaging (3T MRI) and 1H-MRS including the head of each hippocampus. Concentrations of Glu (Glutamate), Glx (Glutamate + Glutamine), NAA (N-Acetyl-aspartate), total-NAA (N-Acetyl-aspartate + N-Acetyl-aspartyl-Glutamate), Cho (Glycerophosphocholine and Phosphocholine compounds), Cr (Creatine) and MI (mionositol) were measured (mmol/l). Hippocampal volumes were additionally calculated using an automated procedure (Freesurfer).

Results
CS patients had lower NAA than controls in the left and right hippocampus (5.2 ± 1.0 vs 6.1 ± 0.7, P < 0.05; 4.9 ± 0.8 vs 6.1 ± 0.6, P < 0.001 respectively), and lower total-NAA in the right (5.7 ± 0.9 vs 6.3 ± 0.9, P < 0.05), suggesting neuronal dysfunction/loss. CS patients had higher GxS than controls in both hippocampi (10.4 ± 1.9 vs 8.6 ± 1.4, P < 0.01; 9.9 ± 1.6 vs 8.9 ± 1.3, P < 0.05 respectively), suggesting gial proliferation, as a repair mechanism after neuronal dysfunction. No differences were found in the other brain metabolites, and there were no differences in left (3815.78 ± 502.96 mm3) and right (3980.75 ± 369.44 mm3) total hippocampal volumes between CS patients and controls (3945.08 ± 408.90 and 4108.39 ± 365.11 mm3, respectively).

Conclusion
Persistently abnormal metabolites are evidenced in the hippocampi of CS patients despite endocrine cure. These functional alterations could be early markers of glucocorticoid neurotoxicity and would precede hippocampal volume reduction.

DOi: 10.1530/endoabs.32.OC4.4

OC4.5 – ESE Young Investigator Award

Influence of somatic mutations on the lateralization index of adrenal vein sampling in aldosterone producing adenosmas
Andrea Olwald1, Evelyn Fischer1, Martin Biblingmaier4, Anna Pallarf1, Christoph Degenhart2, Felix Beuschlein1 & Martin Reincke1
1Medizinische Klinik und Poliklinik IV, Munich, Germany; 2Institut für Klinische Radiologie, Munich, Germany.

Adrenal vein sampling (AVS) is a technically demanding procedure required for identification of suitable candidates for unilateral adrenalectomy in primary aldosteronism. Recently, somatic mutations in aldosterone producing adenosmas (APA) have become a focus of research. We identified KCNJ5 K+ channel mutations in 34% of APAs, and more recently mutations in 2 ATPase family members in 11 and 6%. However, it is unclear whether steroid gradients during the AVS are influenced by the mutation status of the APA. This might have impact on final diagnosis and treatment.

To analyse the influence of somatic mutations on gradients in AVS, 39 patients with APAS diagnosed according to the German Conn Registry standard were studied. All subjects underwent technically successful AVS (with a selectivity index > 2) and had a mutation analysis in tumor tissue. The mutation status of the APAS was: 11 KCNJ5 mutations (6 G151R, 5 L166R), 8 ATPase mutations (5 ATP1A1, 3 ATP2B3) and 20 with none of these mutations.

 Patients with ATPase mutations showed higher blood pressure and lower potassium levels than those with KCNJ5 mutation or no mutation. Lateralization indexes of ATPase mutation carriers were 55.8 ± 23.4 compared to 27.8 ± 11.6 in KCNJ5 mutation carriers and 27.7 ± 9.1 in KCNJ5/ATPase negative patients (P = n.s.). Contralateral suppression (ratio of plasma aldosterone to cortisol of the contralateral side and aldosterone to cortisol in the periphery) was most distinct in ATPase mutated patients with marginal significance (ATPase 0.2 ± 0.1, KCNJ5 0.6 ± 0.2, KCNJ5/ATPase non-mutated 0.8 ± 0.2, P = 0.065).

In summary, ATPase mutations seem to be associated with a higher lateralization of aldosterone production. In contrast to prior findings we did not confirm higher lateralization indexes in KCNJ5 mutated patients. However, further studies with a higher number of patients being included are required.

DOi: 10.1530/endoabs.32.OC4.5

Endocrine Abstracts (2013) Vol 32
OC4.6
9-cis retinoic acid, a novel treatment option for adrenocortical cancer? in vitro and in vivo studies
Diana Rita Szabo1, Kornelia Baghy1, Peter M Szabo2, Andras Falus1, Granda, Ospedale Maggiore Policlinico, Milan, Italy. 1Semmelweis University, Budapest, Hungary; 2Hungarian Academy of Sciences, Budapest, Hungary.

Background
The medical treatment options of adrenocortical cancer are limited. In our previous meta-analysis of adrenocortical tumor genomics data, adrenocortical cancer was found to be associated with reduced retinoic acid production and retinoid X receptor-mediated signaling.

Objective
To study the potential antitumoral effects of 9-cis-retinoic acid (9-cisRA) on the adrenocortical cancer cell line NCI-H295R and in a xenograft model.

Methods
Cell proliferation (flow cytometry), hormone secretion (cortisol, dehydroepiandrosterone, aldosterone) and gene expression (microarray) have been studied in the NCI-H295R cell line. A complex bioinformatics approach involving pathway and network analysis and comparison to previously published microarray studies have been performed. Selected genes were validated by real-time qRT-PCR. Azythic nude mice xenografted with NCI-H295R were used in a small pilot in vivo xenograft model for the study of 9-cisRA on tumor growth.

Results
9-cisRA significantly decreased cell viability and steroid hormone secretion in a concentration- and time-dependent manner in the NCI-H295R cell line. Four major molecular pathways have been identified by the analysis of gene expression data. Ten genes involved in: i) steroid hormone secretion (HSD3B1, HSD3B2), ii) retinoic acid signaling (ABCA1, ABCG1, HMGR), iii) cell cycle damage (GADD45A, CCNE2, UHRF1) and iv) immune response (MAP2K6, IL1R2) were successfully validated. 9-cisRA appears to directly influence cell cycle by network analysis. In the in vivo xenograft model 9-cisRA reduced tumor growth, as well.

Conclusions
9-cisRA might represent a promising new candidate in the treatment of hormone-secreting adrenal tumors and adrenocortical cancer.

DOI: 10.1530/endobs.32.OC4.6

Reproduction
OC5.1
BMP15-dependent gene-expression profiling in human granulosa cells
Raffaella Rossetti1, Davide Gentilini2, Elena Beccaria3, Alessio Paffoni4 & Luca Persani1,1
1Department of Clinical Sciences and Community Health, Laboratory of Endocrine and Metabolic Research, University of Milan, Milan, Italy; 2Laboratory of Molecular Biology, IRCCS Istituto Auxologico Italiano, Cusano Milanino, Italy; 3Division of Endocrine and Metabolic Diseases and Laboratory of Endocrine and Metabolic Research, IRCCS Istituto Auxologico Italiano, Milan, Italy; 4Infertility Unit, Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico, Milan, Italy.

The oocyte-derived growth and differentiation paracrine factor BMP15 has emerged as an essential regulator of the ovarian folliculogenesis, from evidences in animal models (knockout mice and sheeps with naturally occurring mutations) and humans. Indeed, several BMP15 mutations have been identified in association with primary ovarian insufficiency (POI), a heterogeneous and frequent fertility disorder characterized by the premature depletion of ovarian follicles in women <40 years. Despite the frequent inheritability of POI, genetic alterations still explain only few cases and we hypothesized that the elucidation of the BMP15-dependent effects on granulosa cells (GCs) would give interesting insights for advancements in this direction. Through a global approach for large-scale gene-expression profiling, the analysis of the transcriptome induced by recombinant human BMP15 acting on primary cultures of human Granulosa Cells (GCs) was performed. The GCs were obtained from fertile women undergoing IVF and then stimulated in triplicates with BMP15. Treated and untreated GCs were harvested after 0, 2 and 6 h, to evaluate early and late regulated genes. RNAs from each condition were processed for hybridization on Illumina beadchips. Statistical analysis identified about 100 differentially expressed genes (FDR q-value <0.001) already 2 h after treatment (cutoff fold-change >2). As expected, we found that BMP15 induces genes important for the modulation of the BMP/TGFbeta signaling. Interestingly, BMP15 inhibits the GCs expression of genes important for ovarian physiology (folliostatin, TGFbeta3, steroidogenesis enzymes and metalloproteases family members) and regulates apoptotic and proliferative genes (BCL and MAPK families), thus indicating BMP15 as a master regulator of folliculogenesis processes. In conclusion, this is the first comprehensive panel of transcriptomic effects induced by BMP15 on human GCs. The analysis of such regulated genes should allow the selection of novel candidates to be screened in POI cohorts for the comprehension of the pathogenic mechanisms underlying POI.

DOI: 10.1530/endobs.32.OC5.1

OC5.2
The (TTAAAA)n polymorphism in the SHBG gene is related to prenatal androgenization of female fetus: possible implications of the developmental origin of metabolic disorders
Christina Pamporaki1, Nectaria Xita1, Leonards Lazaro3, George Makridimas2, Ioannis Georgiou2, George kolios4, Nikolaos Plachouras5 & Agathocles Tsatsoulis1
1Department of Endocrinology, Medical School, University of Ioannina, Ioannina, Greece; 2Department of Obstetrics and Gynecology, Medical School, University of Ioannina, Ioannina, Greece; 3Laboratory of Human Reproductive Genetics, Medical School, University of Ioannina, Ioannina, Greece; 4Laboratory of Biochemistry, University Hospital of Ioannina, Ioannina, Greece.

Introduction
The aim of this study was to examine whether the distribution of SHBG (TTAAAA)n repeat variants contributes to the exposure of the female fetus to androgen excess, by influencing the, in utero, androgen availability.

Methods
The study population consisted of 100 pregnant women that carried female fetuses and underwent the procedure of amniocentesis due to age (older than 35). Blood samples and amniotic fluid samples were drawn for the measurement of SHBG, testosterone (T) and estradiol (E2). DNA was extracted from peripheral blood leucocytes and amniotic cells and the SHBG (TTAAAA)n genotyping was genotyped by PCR. 53 of the women enrolled in the study population went into labor few weeks later in the same Department. The exact birth weight of their female neonates was recorded.

Results
Women with long SHBG alleles (8/8, 8/9, 10/9, 9/9, 10/10) presented lower levels of SHBG in the amniotic fluid compared to those with shorter alleles (6/6, 6/7, 6/8, 7/7, 7/8) (P=0.027). Moreover, homozygous for the allele 8, 9 and 10 TAAAA repeats (8/8, 9/9, 10/10) had higher T/ShBG ratio in amniotic fluid than heterozygos and those with shorter alleles (P=0.016). A positive correlation between the birth weight of the female neonates and maternal SHBG was also recorded (r=0.292, P=0.032).

Conclusion
The presence of long (TTAAAA) SHBG alleles is associated with lower SHBG levels and higher T/ShBG ratio in the amniotic fluid of female fetuses at midgestation. In addition, lower levels of maternal SHBG are related to lower birth weight of female neonates. Thus, SHBG variants may provide a genetic link to the developmental origin of metabolic disorders and in particular to that of PCOS in women.

DOI: 10.1530/endobs.32.OC5.2

OC5.3
Age-related hormonal and metabolic alterations in women with polycystic ovary syndrome (PCOS)
Pekka Pinola1, Észter Vanky2, Inger Sundstro¨m-Poromaa3, Christina Pamporaki1, Nectaria Xita1, Leandros Lazaros3, Elisabeth Stener-Victorin4, Johanna Puurunen4, Terhi Piltonen4, Katri Punnka5, Jaha Tapanainen6 & Laure Morin-Papunen1
1Department of Obstetrics and Gynecology, University Hospital of Oulu, Oulu, Finland; 2Department of Obstetrics and Gynecology, St Olav’s University Hospital Trondheim, Trondheim, Norway; 3Department of Women’s and Children’s Health, Uppsala, Sweden; 4Department of Physiology/Endocrinology, Institute of Neuroscience and Physiology, Göteborg, Sweden; 5Department of Clinical Chemistry, University of Oulu, Oulu, Finland; 6Department of Obstetrics and Gynecology, University of Helsinki, Helsinki, Finland.

Introduction
PCOS is an age-related hormonal and metabolic alterations seem to persist later in life. The aim was to investigate age-related hormonal and metabolic parameters in PCOS and in healthy women in order to determine cut-off values predicting PCOS.

Endocrine Abstracts (2013) Vol 32
Subjects and methods
PCOS women and 230 healthy controls were divided accordingly: 18–24, 25–29, 30–34, 35–39, 40–44, 45–49 and >50 years. A particular interest was to analyze serum testosterone (T) levels using the golden standard method, liquid chromatography-tandem mass spectrometry (LC-MS).

Results
In PCOS group, there was a U-shaped pattern (decrease towards menopause and increase thereafter) in serum androgens and free androgen index (FAI) while in controls a significant decrease with age in dehydroepiandrosterone sulphate and androstenedione (A), and an increase in FAI were observed. T and FAI were significantly higher in PCOS compared to controls in age groups 18–38 years and 18–44 years, respectively (*P* < 0.001, BMI adjusted).

Serum insulin levels and HOMA-IR were significantly higher in PCOS in all age groups except 45–49 years however, the differences disappeared after BMI adjustment except in women >50 years (12.9 vs. 5.7 mIU/l, *P* = 0.02). Triglycerides were higher and HDL tended to be lower in PCOS especially in women <40 years, and hs-CRP levels were increased in women with PCOS <50 years, but these differences disappeared after BMI-adjustment.

The three best predicting factors for PCOS were FAI (≥2.0, OR 8.18), A (≥9.7 nmol/l, OR 6.16) and T (≥1.1 nmol/l, OR 4.17).

Conclusion
The analyses performed with LC-MS confirm the results of earlier studies using RIAs or other older methods, showing that increased serum T levels in PCOS persist until menopause. The results also indicate that FAI and serum androgens serve as the best predictors of PCOS at all ages, while the prediction value of metabolic factors do not perform equally well as they may associate more with obesity than with PCOS per se.

DOI: 10.1530/endoabs.32.OC5.3

OC5.5
FSHB – 211 and FSHB 2039 polymorphisms are associated with serum levels of FSH, AMH and age of pubertal onset in 78 healthy girls: a longitudinal cohort study
Casper P Hagen1, Lise Akgård1, Kaspar Sørensen1, Annette Mouritsen1, Mikkel G Mieritz2, Katharina M Main1, Kristian Almstrup1, Ewa Rajpert-De Meyts1, Richard A Anderson2 & Anders Juul1
1Department of Growth and Reproduction, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; 2Medical Research Council Centre for Reproductive Health, University of Edinburgh, Edinburgh, UK.

Context
Potency of the FSH-pathway varies according to polymorphisms in the promoter of the gene encoding the FSH beta subunit (FSHB – 211 G > T, rs10835638) and in the gene encoding the FSH receptor (FSHR 2039 A > G, rs6166). A recent study suggested that carriers of the combination of FSHB GG and FSHR AA had the most reproductive ‘fit’ phenotype (higher serum FSH and a more sensitive FSH receptor). In pre-pubertal girls, FSH and AMH levels correlate negatively indicating a pituitary–gonadal set-point.

Objective
To evaluate if polymorphisms in FSHB and FSHR were associated with reproductive parameters in healthy girls.

Design and setting
Seventy-eight healthy girls were examined biannually in the COPENHAGEN Puberty Study; number of examinations per girl, median (range), 9 (2–13). Serum levels of hormones were measured by immunoassays. Genotyping was determined by PCR amplification followed by restriction enzymes specific for the genotypes (RFLP analysis).

Main outcome measures
Association analyses of single and combined polymorphisms with FSH, AMH, and age at pubertal onset.

Results
Carriers of (FSHB GG + FSHR AA) had higher levels of FSH prior to pubertal onset, lower mean serum levels of AMH, and they entered puberty earlier than girls with other combinations of genotypes; FSH 2.2 (1.3–3.9) vs 1.5 (0.4–4.4) IU/l (P = 0.05), AMH 13.8 (5.6–53.9) vs 19.4 (4.8–47.4) pmol/l (P = 0.04), and age of pubertal onset 9.7 (8.8–10.7) vs 10.6 (9.0–13.5) years (P = 0.03), respectively.

Conclusions
Our findings indicate that genetic polymorphisms in the FSH pathway influence timing of puberty in healthy girls, as well as the pre-pubertal FSH-AMH set-point. Furthermore, it seems that individual AMH levels are determined by common variations in genes regulating follicle growth as well as the number of resting primordial follicles.

DOI: 10.1530/endoabs.32.OC5.5

OC5.6
INSL3 in 268 male patients with congenital hypogonadotropic hypogonadism (CHH): effects of different modalities of hormonal treatment
Séverine Trabado1, 2, Luigi Maione1, 3, Julie Sarfati1, Sylvie Salenave3, Philippe Chanson1, 3, Sylvie Brailly-Tabuteau1, 2, Jacques Young1, 3 1UMR-S693, Faculté de Médecine Paris-Sud, Univ Paris-Sud, Le Kremlin Bicêtre, France; 2Service de Gynécologie Moléculaire, Pharmacogénétique et Hormonologie, Hôpital Bicêtre; Assistance Publique-Hôpitaux de Paris, Le Kremlin Bicêtre, France; 3Service d’Endocrinologie et des Maladies de la Reproduction, Hôpital Bicêtre, Assistance Publique-Hôpitaux de Paris, Le Kremlin Bicêtre, France.

Context
Inulin-like peptide three (INSL3) is a testicular hormone, secreted by Leydig cells, during fetal life, in newborns, and after puberty. These 3 phases of testicular activation are impaired in CHH.

Objective
To evaluate in a single center circulating INSL3 in a significant series of men with CHH in order to assess the consequences of pre- and postnatal gonadotropin deficiency, to specify the INSL3 regulation by gonadotropins and to evaluate the potential diagnostic interest of this peptide.

Patients
Two hundred and sixty-eight CHH patients (77 untreated, 97 receiving testosterone and 94 under combined gonadotropin therapy (bCG and FSH)) and 40 age-matched normal men were evaluated.

Methods
Serum INSL3 was immunoaassayed by a validated sensitive and specific RIA.

Endocrine Abstracts (2013) Vol 32
Results
Mean INSL3 levels (±s.d.) were 827±364 pg/ml in normal men and dramatically decreased (61±42 pg/ml; P<0.001) in untreated CHH patients, all of whom had values below controls. Positive correlations between both serum total testosterone (T) or LH and INSL3 (respectively P<0.01 and P<0.0001) were observed in untreated CHH. In T treated CHH mean INSL3 was also very low (50±25 pg/ml) but in CHH receiving combined hCG and FSH therapy, INSL3 was very significantly higher (402±292 pg/ml; P<0.001) than in untreated CHH. Combined FSH-hCG therapy (from 61±21 to 301±254 pg/ml) or hCG alone (from 48±10 to 223±114 pg/ml) significantly and prospectively increased INSL3 levels in CHH, contrary to T (from 61±21 to 53±37 pg/ml) or FSH monotherapies (from 48±10 to 60±16 pg/ml).

Conclusions
The dramatic INSL3 decrease in CHH is caused by LH deficiency and correlated with its severity. The increase in INSL3 levels during combined gonadotropin and hCG monotherapy reinforces its exclusive Leydigian origin and its positive regulation by LH/hCG. Finally, INSL3 seems as sensitive as total testosterone to evaluate the testicular Leydig function in CHH and is therefore a useful diagnostic marker.

DOI: 10.1530/endoabs.32.OC6.6

Diabetes & Obesity

Type 2 diabetes is one of the most common health problems worldwide and its prevalence is rapidly increasing. Although environmental factors play a substantial role in the etiology, genetic susceptibility has been established as an important risk factor. Several recent genome-wide studies and linkage analysis testing have identified and confirmed various T2D susceptibility loci. However, as demonstrated by the results of the HapMap project and by other studies, the allele frequencies of the risk variants differ between populations.

As a preliminary study of the genetic risk evaluation in Portuguese T2D patients, we selected 18 variants that have been consistently associated with T2D (PPARG, KCNJ11, TCF7L2, WFS1, KCNQ1, HNF1B, HHEX, NOTCH2, CDC123, PPARgamma and CD36, while muscle and liver SCD-1 levels were 4-fold upregulated in KO. The expression of G-6-Pase, key gluconeogenic enzyme, was higher in KO compared to WT mice. Taken together, our data show dissociation between DIO and IR in AHNAK KO mice. AHNAK has an important role in weight control, but AHNAK deficiency impairs insulin sensitivity in vivo. Therefore, careful regulation of AHNAK is essential for the management of metabolic homeostasis.

Glucagon-like peptide-1 (GLP-1) is an incretin hormone with multiple actions besides control of glucose homeostasis. GLP-1 is known to cause natriuresis in humans but the effects on basic renal physiology are still partly unknown. This study therefore aimed to demonstrate the effects of GLP-1 on kidney hemodynamics, electrolyte handling, and the renin-angiotensin-aldosterone system in healthy men. Twelve healthy young males were examined in a randomized, controlled, double-blinded, single-day, cross-over trial to evaluate the effects of two hours GLP-1 infusion on kidney functions. Glomerular filtration rate (GFR) and renal plasma flow (RPF) were assessed with 125I-hippuran, respectively, using a constant infusion renal clearance technique based on timed urine sampling. GLP-1 had no significant effect on either GFR (+1.9%, 95% CI (−0.8; 4.6%)) or RPF (+2.4%, 95% CI (−3.6; 8.8%)). Fractional urine excretion of lithium increased 9% (P=0.001) and renal sodium clearance increased 37% (P=0.0007). Angiotensin II decreased 19% (P=0.003) while renin, aldosterone, and the urinary excretion of angiotensinogen showed no significant changes.

The results indicate that although GLP-1 markedly reduces proximal tubule sodium reabsorption, the acute effects on GFR and RPF are very limited in healthy humans. The finding of GLP-1’s ability to reduce angiotensin II concentration is novel and may play a part in the possible kidney protective properties of GLP-1.

Endocrine Abstracts (2013) Vol 32

Reduction of fat mass with the mTOR inhibitor, sirolimus, in humans: from transplantation to lipodystrophies

Emilie Parent1, François Pattou1, Olivier Ernst1, Georges Lion1, Isabelle Wolowczuk2, Olivier Dhurancy1, Christian Noel1, Julie Kerr-Conte2 & Marie-Christine Vantyghen1,3
1Regional University Hospital, Lille, France; 2Pasteur institute, UMR 8199, Lille, France; 3INSERM UMR 859, Lille, France.

Objectives
Sirolimus inhibits adipocyte differentiation (Yeh PNAS 1995). This study compares weight and fat markers in two groups of patients treated or not with sirolimus, before and after transplantation.

Patients and method
Nineteen islet-alone transplanted patients treated with sirolimus and 7 islet-alone or liver-transplanted patients NOT treated with sirolimus were compared 1 year after transplantation in terms of weight, fat mass (equation of body fat and percentage of fat mass by DXA), and metabolic parameters.

DOI: 10.1530/endoabs.32.OC6.6

Endocrine Abstracts (2013) Vol 32

Dissociation between high fat diet-induced obesity (DIO) and insulin resistance: lessons from AHNAK knockout mice

Mays Ramada1, Chava Harel1,2, Natalia Krits1,2, Michail Armoni1,2 & Eddy Karnieli1,2
1Technion, Israel Institute of Technology, Haifa, Israel; 2Rambam Medical Center, Haifa, Israel.

Obesity is usually considered to be a forerunner to insulin resistance (IR). Using in vitro studies, we have identified a role for the giant protein AHNAK in regulating Glut4 expression and function. Ex vivo analysis of white adipose tissue from ob/ob mice and aged/obese rats exhibited elevated AHNAK protein levels (2.3- and 3-fold) with concomitant reduction in Glut4 levels (5- and 2-fold).

The aim of this study was to investigate the role of AHNAK in overall metabolic homeostasis using AHNAK knockout (KO) mice. When challenged with high-fat diet-chow for 12 weeks, AHNAK KO mice were protected from DIO as reflected by a 50% reduced adipose tissue mass, 25% reduced body weight and 37% increased lean body mass, compared to wild type (WT) mice on HFD. KO mice exhibited IR as evident from their glucose (AUC 28412 vs 34307) and insulin (AUC 12645 vs 15035) tolerance tests. Fasting blood glucose levels were 17% elevated while plasma insulin levels were 37% reduced in KO-HFD compared to WT-HFD. Contrary to the in vitro results, Glut4 levels in adipose tissue obtained from either KO-chow or KO-HFD were 35% and 20% reduced compared to WT-chow. Real-time PCR analysis showed no change in levels of adipogenic genes PPARGamma and CD36, while muscle and liver SCD-1 levels were 4-fold upregulated in KO. The expression of G-6-Pase, key gluconeogenic enzyme, was higher in KO compared to WT mice. Taken together, our data show dissociation between DIO and IR in AHNAK KO mice. AHNAK has an important role in weight control, but AHNAK deficiency impairs insulin sensitivity in vivo. Therefore, careful regulation of AHNAK is essential for the management of metabolic homeostasis.

DOI: 10.1530/endoabs.32.OC6.2

Endocrine Abstracts (2013) Vol 32
islet-alone transplanted patients treated with sirolimus were reassessed 5 years post-transplantation.

Results
Before transplantation, the metabolic and weight/fat parameters were similar in the 2 groups except for C-peptide. One year post-transplantation, body fat and leptin reduction was more important in the sirolimus than in the NON-sirolimus group ($P<0.05$). Leptin levels were lower in the sirolimus group ($P<0.01$). Compared to pre-transplant values, one year post-transplantation, weight, fat mass and metabolic parameters did not change in the NON-sirolimus group while the sirolimus group showed a significant reduction in weight ($P<0.001$), BMI ($P<0.001$), body fat ($P<0.001$), percentage of body ($P<0.05$) and truncal ($P<0.05$) fat mass, HbA1c levels ($P<0.001$) and fiscore ($P<0.01$). Compared to pre-transplant values, the sirolimus group showed a significant reduction of leptin level one ($P=0.004$) and five years ($P=0.01$) post-transplantation, as well as a persistent reduction of HbA1c (before: 8.4 (1.5); 1-year: 5.8 (1.7); 5-years 6.7 (1.7)% and fiscore (before: 0.0; 1-year: 7.0 (3.5); 5-years 4.0 (4.0)) ($P<0.05$). Sirolimus correlated with leptin ($r=-0.22$, $P=0.018$) and body fat mass ($r=-0.18$, $P=0.03$).

Conclusion
These results suggest that sirolimus modulates the amount and/or the quality of adipose tissue and innate immunity, opening new perspectives both in the choice of immuno-suppressant, and the treatment of nucleopathies, especially lipodystrophies (Ramos Sci Transl Med 2012).

DOI: 10.1530/endoabs.32.OC6.4

OC6.5 – ESE Young Investigator Award
The role of costimulatory molecules B7.1 and B7.2 in obesity-related adipose tissue inflammation and liver steatosis
Antonios Chatzigiorgiou1 2, Kyong-Jin Chung1 2, Ruben Garcia Martin1 2, Julia Phiel1 2, Sylvia Grossklau1 2, Stefan R Bornstein1, Theodora Tzanavari1, Katia Karalis1 2 & Triantafyllos Chavakis1 2
1Department of Internal Medicine III, Dresden University of Technology, Dresden, Germany; 2Institute of Physiology, Dresden University of Technology, Dresden, Germany; 3Developmental Biology Section, Biomedical Research Foundation of the Academy of Athens, Greece.

Introduction
Macrophages and lymphocytes are considered as major players in adipose tissue and innate immunity, opening new perspectives both in the choice of immuno-suppressant, and the treatment of nucleopathies, especially lipodystrophies (Ramos Sci Transl Med 2012).

Results
B7.1 and B7.2 expression was upregulated in gonadal AT and SVF upon HFD. Dko mice displayed higher glucose, cholesterol and leptin levels and worse GTT when fed a HFD compared to the B7.1/B7.2 sufficient mice. This was accompanied by downregulation of Tregs, CD4 and CD8 lymphocytes and a parallel upregulation of proinflammatory M1 macrophages (defined as F4/80 + CD11b + CD11c + or F4/80 + CD11c + CD206-cells) in both subcutaneous and gonadal AT. Dko mice showed also increased liver steatosis, linked with increased levels of inflammatory M1-like macrophages and reduced levels of Tregs in the liver. In accordance, Dko mice had higher levels of inflammation and fat accumulation genes in AT and liver respectively and lower levels of UCP-1 in the brown AT.

Conclusion
The B7.1-B7.2 signalling pathways are significant regulators of the obesity-related adipose tissue inflammation and liver steatosis pathophysiology.

DOI: 10.1530/endoabs.32.OC6.5

OC6.6
Serum- and glucocorticoid-regulated kinase 1 in obesity-related adipose tissue and peripheral inflammation
Marie Helene Reiter, Florian Kiefer, Maximilian Zeyda, Chantal Kopecky, Thomas Stulnig, Anton Luger & Greisa Vila

see P728.

DOI: 10.1530/endoabs.32.P728
Nurse Posters
N1
Pegvisomant home care program is likely to improve treatment compliance leading to rapid IGF1 control
Els Rutten1, Dushy Husein1, Pascale Abrams2, Linsey Winne3, Els Feyen1 & Guyl T’Sjoen1
1Department of Endocrinology, University Hospital Ghent, Gent, Belgium; 2Sint Augustinus Hospital, Wilrijk, Belgium; 3AZ Damiaan Hospital, Oostende, Belgium.

Background
Pegvisomant has demonstrated efficacy in attaining IGF1 normalisation in previously uncontrolled acromegalic patients. Improper or less than prescribed use may lead to suboptimal control.

Aim
Evaluation of home educational program.

Methods
Multicenter Flemish study in seven non-controlled acromegalic outpatients. All patients were trained for daily s.c. pegvisomant injection at home by one single 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, and 18. Preliminary results include IGF1 at baseline, 3 and 4.5 months.

Results
Seven acromegalic patients uncontrolled with octreotide LAR (n = 4; 30 mg monthly) or lanreotide (n = 3; 120 mg per 3 weeks or monthly) were included in this observational study. Upon dose adjustment from 10 OD to 20 mg OD for patient 1 IGF1 at 4.5 months further decreased to 152. For patients 2 and 5 IGF1 further decreased without dose titration to 253, and 107 respectively. No adverse events were recorded, except for more frequent hypoglycemic episodes in 1 insulin-treated woman with type 2 diabetes.

Table 1

<table>
<thead>
<tr>
<th>Age (gender)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pegvisomant starting dose (mg)</td>
<td>10 OD</td>
<td>10 OD</td>
<td>10 OD</td>
<td>10 EOD</td>
<td>10 OD</td>
<td>10 OD</td>
<td>10 OD</td>
</tr>
<tr>
<td>IGF1 baseline (ng/ml)</td>
<td>347</td>
<td>1032</td>
<td>311</td>
<td>289</td>
<td>299</td>
<td>877</td>
<td>341</td>
</tr>
<tr>
<td>IGF1 3 months later (ng/ml)</td>
<td>326</td>
<td>335</td>
<td>157</td>
<td>93</td>
<td>124</td>
<td>280</td>
<td>50</td>
</tr>
</tbody>
</table>

M, male; F, female; OD, once daily; EOD, every other day.

Conclusion
In all participants IGF1 decreased significantly (P = 0.018) within a time period of 3 months. Working with a specialist nurse may prove a key to success in attaining rapid IGF1 normalisation, due to enhanced patients’ compliance.

DOI: 10.1530/endoabs.32.N1

N2
Psychiatric morbidity in pediatric patients after surgical remission of Cushing’s disease: case presentations
Margaret Keil, Celia Ryder & Constantine Stratakis
National Institutes of Health, NICHD, Bethesda, Maryland, USA.

Context
Endogenous Cushing’s syndrome (CS) may have different effects in children than what has been described in adults. Prior studies of children and adolescents with CS have identified cognitive decline despite reversal of brain atrophy after remission of CS, as well as residual impairment in quality of life measures. Although the observations of parents of children and adolescents with CS support personality changes, significant psychopathology has not been described in the literature.

Setting
Subjects were enrolled in a clinical protocol at the National Institutes of Health Clinical Center in Bethesda, MD, USA.

Clinical presentation
We report six children (4M, 12.4 ± 2.5 years), who underwent successful transsphenoidal surgery (TSS) for treatment of Cushing’s disease (CD), and subsequently developed significant affective symptoms (range for onset of symptoms 4–60 months). Affective symptoms included: decline in school performance, anger/rage outbursts, suicidal ideation, anxiety, and depression. One child (18 years old female), who committed suicide 60 months post-TSS, had recently discontinued antidepressant medication. She had a history of anxiety during active CS and was treated with an anxiolytic. The 4 patients with onset of symptoms within 7 months of TSS were on glucocorticoid replacement, and 1 year follow-up evaluation showed recovery of HPA axis and biochemical evidence of remission. The two patients who presented with onset of symptoms 48 months or later, underwent endocrine evaluation that showed biochemical evidence of remission and normal anterior pituitary hormone levels.

Conclusion
A longitudinal study of adults reported an incidence of psychopathology of 66.7% in active CS that declined to 24.1% at 12 month after remission (Dorn 1997). This is the first report of affective symptomatology/behavioral dysregulation, including suicidal ideation, in a subgroup of children and adolescents after remission of CS. Health care providers should screen for changes in symptomatology, including suicidal ideation, anger outbursts, anxiety, and depression and refer to appropriate mental health professionals.

DOI: 10.1530/endoabs.32.N2

N3
Living in the shadow and light: Iranian youths’ response to diabetes-related stigma
Samereh Abdoli1, Mehri Doosti Irani2, Soroor Parvizi3, Naeimeh Seied Fatemi3, Masood Amini2 & Bijan Iraj4
1Faculty of Nursing and Midwifery, Nursing and Midwifery Care Research Centre, Isfahan University of Medical Sciences, Isfahan, Iran; 2Faculty of Nursing and Midwifery, Isfahan University of Medical Sciences, Isfahan, Iran; 3Faculty of Nursing and Midwifery, Tehran University of Medical Sciences, Tehran, Iran; 4Endocrinology and Metabolism Research Centre, Isfahan University of Medical Sciences, Isfahan, Iran.

Introduction
Diabetes is one of the most acceptable chronic diseases. However, diabetes-related stigma is proposed as an important and striking phenomenon in many countries especially in Asian countries such as Iran. This study aimed to explore the responses of Iranian young people with type 1 diabetes to the diabetes-related stigma.

Methods
Conventional qualitative content analysis approach guided this inquiry. Volunteered people with type 1 diabetes were recruited by purposeful sampling from one endocrine and metabolism center in Isfahan in 2012. Data gathering was done through 17 individual unstructured in-depth interviews and three focus groups. Data saturation was achieved through 33 participants. The data were analyzed using qualitative content analysis.

Results
All participants acknowledged stigma and responded it in different ways, which was categorized in two main categories including living in the shadow (hide and seek, missing diabetes, withdrawal) and moving toward light (diabetes disclosure, destruction of the false bubbles).

Conclusion
The most response especially for girls was to live in the shadow of silence that can be associated with negative consequences affecting diabetes management. Moving towards the light, suggests that it is possible to help people with type 1 diabetes to achieve a normal life as much as possible. It is necessary to plan the anti-stigma programs and engage them actively to reduce stigma and mitigate or prevent its negative impacts.

Keywords
Diabetes-related Stigma, People with Type 1, IRAN.

DOI: 10.1530/endoabs.32.N3

N4
Nurse led telephone clinic: antenatal hypothyroidism
Claire Goodhart
UCLH, London, UK.

Background
Hypothyroidism is characterised by insufficient secretion of the thyroid and its detection measured by elevated serum TSH levels. Although relatively common during pregnancy, untreated maternal hypothyroidism is associated with adverse obstetric and neonatal outcomes such as...
preeclampsia, placental abruption and miscarriage, or fetal neurodevelopment defects.
Highlighting a nurse led specialised telephone clinic in the close monitoring and care of these women is vital.

Aims
To provide for pregnant women with hypothyroidism a specialised Nurse-led Clinic, with structured pathways, in collaboration with multidisciplinary teams, to ensure:

- Continuity of care with reduction in requirement for face-to-face appointments.
- A streamlined service supported by evidence based practice.
- Earlier detection of elevated TSH levels above 2.5 IU/l.
- Optimising treatment management.
- Providing support and education, enhancing adherence and reducing non-attendance.

Structure:
- Referral of women with history of hypothyroidism, or TSH levels above 2.50 IU/l.
- Medical history and results discussed with physician.
- Appointments booked within 2 weeks where condition education, support and treatment management are reviewed.
- Electronic recording of visit.
- On-going review throughout each trimester prior to discharge.

Caseload
Seventy-three new referrals were reviewed over a 3-month period, of those 30% within their first-trimester, and 44% in their second trimester presented, with elevated TSH levels above 2.5 IU/l on referral.
This reflects positive identification patients at risk, due to improved multi-disciplinary team communication facilitated by the specialist nurse.

Conclusion
Standardised protocols ensure earlier referral; resulting in the provision of high-quality patient focused Nurse-led care, treatment management and patient education of gestational hypothyroidism. Through a service systematically developed for continual improvements that are directly relayed to the patients, while providing a cost effective service for patients and service providers, while ensuring nursing activity is recorded and can be audited.

DOI: 10.1530/endoabs.32.N4

N5
Assessing treatment satisfaction, knowledge and adherence of patients attending a pituitary Nurse-led Clinic
Sofia Llahana
University College Hospital, London, UK.

Background and aim
Polypharmacy is characteristic of endocrine conditions and patients who are satisfied and knowledgeable of their treatment have better outcomes. The aim of this study was to measure treatment satisfaction, knowledge and adherence in patients with a pituitary condition attending a Nurse-led Clinic.

Methods, sample and data collection
Data were collected using a postal survey between January and March 2010 and included a total of 262 patients. The questionnaire which was developed for the purpose of this study includes two subscales; i) the 18-item Satisfaction and Knowledge subscale with a 5-point Likert scale ‘strongly agree to strongly disagree’ and ii) the 8-item Adherence subscale with a 5-point Likert scale ‘never to always’ and a ‘not applicable’ 6th point for patients taking their medication on a weekly/monthly basis. Statistical analysis was performed using SPSS version 19 for Windows.

Results
A response rate of 58% was achieved (n = 152; 84 females and 68 males). Mean age was 42 years (s.d. = 15.7; range = 19–79). Mean duration of diagnosis was 16 years (s.d. = 11.8; range = 1–45). Patients were taking anything from 1 to 6 different medications for their endocrine condition (mean = 2.5; s.d. = 1.5) with almost a third taking between 4 and 6 medications. A high level of Satisfaction and Knowledge was reported (mean = 3.8 (s.d. =0.7); items SUM = 64.6 (s.d. = 11.6) with scoring range 17–85). Similarly, patients reported high levels of Adherence to treatment (mean = 4.1 (s.d. = 0.8); items SUM = 20.3 (s.d. = 0.8) with scoring range 5–25).

Conclusion
The results of this audit emphasise the important role that the Endocrine Nurse plays in patient education and in achieving better treatment satisfaction and adherence.

DOI: 10.1530/endoabs.32.N5
Poster Presentations
Adrenal cortex

P1

Chronocort®, a multiparticulate modified release hydrocortisone formulation, shows dose linearity and twice daily dosing provides physiological cortisol exposure.

Richard Ross1, Martin Whitaker1, Miguel Debono2, Hiep Huatan2, Wiebke Arlt3 & Deborah Merke1

1University of Sheffield, Sheffield, UK; 2Diurnal Ltd, Cardiff, UK; 3University of Birmingham, Birmingham, UK; 4The National Institutes of Health, Bethesda, Maryland, USA.

Cortisol has a distinct circadian rhythm; levels rise from 0300 h to peak within an hour of waking and gradually decline until 1800 h before a quiescent period lasting from 1800 to 0300 h. Current hydrocortisone replacement regimens are unable to replicate this rhythm and we have been investigating modified dosing technology. Our initial formulation, using tabletting technology, demonstrated it was possible to replicate the overnight rise in cortisol but the tablet had reduced bioavailability (Debono et al. Journal of Clinical Endocrinology and Metabolism 2009 94 1548–1554). We have now investigated the use of multiparticulate technology which has flexibility for variable doses using the same formulation. We tested six multiparticulate formulations and identified a formulation, DIURF-006, that provided the optimal overnight cortisol profile. We have now tested dose-proportionality and twice daily dosing for DIURF-006 using 5, 10, and 20 mg administered as a single-dose at night and 30 mg administered as a 20 mg dose at night and a 10 mg dose the following morning in 16 healthy male volunteers in whom endogenous cortisol levels were suppressed with desamethasone. Dosing was randomised, all studies were separated by 1 week wash-out period and cortisol levels measured by LC–MS/MS. Serum cortisol levels were shown to increase linearly with dose, although dose proportionality was not at unity as shown in the slope of the regression line: C max for 5, 10, 20, and 30 mg was 288, 440, 641, and 665 nmol/l (slope: 0.49, 95% CI 0.42–0.56) and AUC 0–t was 1586, 2530, 3919, and 5610 h·nmol/l (slope: 0.69, 95% CI 0.65–0.73). The AUC and C max for twice daily dosing were similar to 0.60 the previously reported for normal diurnal cortisol secretion. In conclusion, Chronocort® formulation DIURF-006, provides a linear increase in C max and cortisol AUC over a dose range from 5 to 30 mg and the C max and AUC are similar to that previously reported for physiological cortisol levels.

Acknowledgements

This research was supported in part by the Intramural Research Program of the NIH.

DOI: 10.1530/endoabs.32.P1

P2

Impaired quality of life in CAH adults is associated with adiposity and insulin resistance.

TS Han1, N Krone2, DS Willis3, GS Conway1, DA Rees4, RH Simson5, BR Walker1, W Arlt3 & RJ Ross1

1University College London, London, UK; 2Birmingham University, Birmingham, UK; 3British Endocrine Society, Bristol, UK; 4University of Cardiff, Cardiff, UK; 5Edinburgh University, Edinburgh, UK; 6Sheffield University, Sheffield, UK.

Background

Quality of life (QoL) has been variously reported as normal or impaired in congenital adrenal hyperplasia (CAH) adults. We found impaired QoL in UK CAH adults (Arlt et al. Journal of Clinical Endocrinology and Metabolism 2010 95 5110–5121) and now report the relationship between QoL (SF-36) and health outcomes in these patients.

Methods

Cross-sectional analysis of 151 CAH adults with 21-hydroxylase deficiency aged 18–69 years. QoL was transformed into age- (decade) and sex-adjusted -scores were used in multiple stepwise regression analysis as predictor variables of QoL.

Results

Three PCs were identified by PCA that explain 61% of the total variance (r2) in observed variables. Regression analysis demonstrated that PC2, reflecting adiposity and insulin resistance (waist circumference, serum triglycerides, HOMA-IR and HDL-cholesterol), related to individual QoL scores, specifically impaired physical function (β=−0.72, 95% CI: −1.11 to −0.34, r2=19.9%, P<0.001), bodily pain (β=−0.51, 95% CI: −0.77 to −0.23, r2=21.6%, P<0.001), general health (β=−0.30, 95% CI: −0.80 to 0.20, r2=16.0%, P=0.001), vitality (β=−0.44, 95% CI: −0.65 to −0.16, r2=15.5%, P=0.002), and the Physical Components Summary Score (β=−0.58, 95% CI: −0.83 to −0.33, r2=26.4%, P<0.001), but not to the Mental Components Summary Score.

Conclusions

Increased adiposity and insulin resistance are associated with impaired QoL in adults with CAH. Intervention studies are now required to establish whether reduction in metabolic risk factors can improve QoL in this disadvantaged patient group.

DOI: 10.1530/endoabs.32.P2

P3

Correlation between cell cycle, steroidogenesis and PKA RIA and RIB subunits in adrenocortical tumors cells.

Francesco Basso1, Neda Rezaei1, Bruno Ragazzoni1, Jerome Berthaler1 & Marthe Rizk-Rabin1

1Institut Cochin INSERM U1016, CNRS UMR8104, Université Paris V, Paris, France; 2Service des maladies Endocrininetens et Métaboliques Hôpital Cochin, Paris, France.

The cyclic AMP (cAMP) signalling cascade is one of the main pathways involved in the pathogenesis of adrenocortical tumors (ACT). PKRα or PKRβRIβ are involved in the proliferation/apoptosis in a subset of tumors. Majors alterations of genes involved in both cell proliferation and the cell cycle have been described by transcriptome and miRNome analysis in various types of adrenocortical tumors (ACC, ACA, AIMAH, and PPNA). In addition to tumor growth for malignant tumors, steroid excess causes morbidity in patients with all types of ACT.

The goal of this study is to find whether there is a correlation between the cell cycle and the steroidogenesis.

Methods

We have studied the cell cycle distribution (FACS) and the expression of the steroidogenic enzymes (western blot, and RT-qPCR) in i) H295R cell line after inactivation of PKRα or PKRβRIβ using RNA interference ii) synchronized H295R cell line, and iii) PPNA cells in primary cell culture. We used pharmacologic drugs to arrest cells at specific cell cycle check point: L-mimosine (G1 phase), aphidicolin (S phase), and nocodazole (G2 phase). The expression of the different actors of cell cycle regulation as cyclins and cyclks, and signalling pathways were studied.

Results

The decrease of either R14 or Rβ2 protein enhances the accumulation of cells in 2 G2 phase, and Cyp17A, Cyp11B1 and Cyp11B2 levels. The synchronization of both the H295R (ACC cells) or PPNA of primary cell culture at G2 phase increased the expression of the steroidogenic enzymes. In PPNA this increase started at the S phase. Arresting both H295R and PPNA cells in G1 phase decreases the steroidogenic enzymes expression, resulting in a decrease in cortisol secretion.

Conclusion

We have found a correlation between the cell cycle check point and the expression of steroidogenic enzymes. Targeting specific cell cycle check point may down regulate the hyper secretion of steroids in these tumors.

DOI: 10.1530/endoabs.32.P3

P4

Long-term follow-up in adrenal incidentalomas: an Italian Multicentre Study.

Valentina Morelli1, Giuseppe Reimondo2, Roberta Giordano3, Silvia Della Casa4, Giovanna Muscogiuri5, Caterina Policola6, Antonio Stefano Salcuni4, Alessia Dolci6, Giulia Beltrami7, Serena Palmieri1, Della Casa4, Giovanna Muscogiuri4, Caterina Policola4, Antonio Stefano Salcuni5, Alessia Dolci6, Giulia Beltrami7, Serena Palmieri1, Stefano Majors alterations of genes involved in both cell proliferation and the cell cycle have been described by transcriptome and miRNome analysis in various types of adrenocortical tumors (ACC, ACA, AIMAH, and PPNA). In addition to tumor growth for malignant tumors, steroid excess causes morbidity in patients with all types of ACT.

The goal of this study is to find whether there is a correlation between the cell cycle and the steroidogenesis.

Methods

We have studied the cell cycle distribution (FACS) and the expression of the steroidogenic enzymes (western blot, and RT-qPCR) in i) H295R cell line after inactivation of PKRα or PKRβRIβ using RNA interference ii) synchronized H295R cell line, and iii) PPNA cells in primary cell culture. We used pharmacologic drugs to arrest cells at specific cell cycle check point: L-mimosine (G1 phase), aphidicolin (S phase), and nocodazole (G2 phase). The expression of the different actors of cell cycle regulation as cyclins and cyclks, and signalling pathways were studied.

Results

The decrease of either R14 or Rβ2 protein enhances the accumulation of cells in 2 G2 phase, and Cyp17A, Cyp11B1 and Cyp11B2 levels. The synchronization of both the H295R (ACC cells) or PPNA of primary cell culture at G2 phase increased the expression of the steroidogenic enzymes. In PPNA this increase started at the S phase. Arresting both H295R and PPNA cells in G1 phase decreases the steroidogenic enzymes expression, resulting in a decrease in cortisol secretion.

Conclusion

We have found a correlation between the cell cycle check point and the expression of steroidogenic enzymes. Targeting specific cell cycle check point may down regulate the hyper secretion of steroids in these tumors.

DOI: 10.1530/endoabs.32.P3
Casa Sollievo della Sofferenza Hospital, IRCCS, San Giovanni Rotondo, Foggia, Italy; 2Unit of Endocrine Disease and Diabetology, S. Giuseppe Hospital, Gruppo Multimedica, University of Milan, Milan, Italy; 3Unit of Endocrinology and Diabetology, Department of Biomedical Sciences for Health, University of Milan, IRCCS Policlinico San Donato, Milan, Italy; 4Division of Endocrinology, Diabetology and Metabolism, Department of Internal Medicine, University of Turin, Turin, Italy.

Introduction
The need of a long-term follow-up in adrenal incidentalomas (AI) is debated and data on cardiovascular events (CVE) are lacking.

Methods
In this retrospective study all patients referred to seven Italian Endocrine Centers for AI, without signs of hypercortisolism at baseline and with a ≥ 5 years follow-up (80.7 ± 30 months, range 60–286), were enrolled. From 171 patients (121 F aged 59.5 ± 10.2 years (range 25–79) the changes in weight, glucose and lipid metabolism, blood pressure control and the occurrence of CVE were obtained. Patients were classified as affected with subclinical hypercortisolism (SH) in the presence of cortisol after 1 mg dexamethasone suppression (1 mg DST) test > 5 μg/dl or ≥ 2 parameters out of low ACTH, increased urinary free cortisol and 1-mg DST > 3 μg/dl.

Results
At baseline SH was found in the 14% of patients. The prevalence of obesity, diabetes mellitus, dyslipidemia, and arterial hypertension (54, 21, 25, and 45% respectively) was not different between patients with (SH+) and without SH (SH–). At baseline SH+ patients showed a higher CVE prevalence than SH– ones (21 vs 7%), regardless of age (OR 3.3, 95% CI 1.0–11.1, P < 0.05). At the end of follow-up a new diagnosis of SH was made in the 7.6% of patients, whereas in the 3.5% the SH diagnosis was not confirmed. The adenoma size (baseline 2.3 ± 0.8 cm) increased > 2.5 cm in the 2.9% of cases. The glucose and lipid metabolism, blood pressure, and weight control worsened in the 24, 16, 36 and 14% of patients, respectively. The SH persistence/appearance was significantly associated with the worsening of ≥ 2 out of the metabolic parameters (P = 0.013) and with the occurrence of new CVE (P = 0.05).

Conclusion
In AI patients a long-term follow-up is recommended for the diameter increase and SH development risk. SH patients are at risk of worsening of the metabolic control and, importantly, of CVE.

DOI: 10.1530/endoabs.32.P4

P6
Activating EGFR promotes ACC cell proliferation by inducing VEGF autocrine secretion
Teresa Gagliano1, Daniela Moli1, Erica Gentili1,2, Mariaenrica Bellio1, Ettore degli Uberti1,3 & Maria Chiara Zaitelli1,2
1Section of Endocrinology, University of Ferrara, Ferrara, Italy; 2Laboratorio in rete del Tecnopolo 'Tecnologie delle terapie avanzate' (LTTA) of the 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 used. 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. Aim of our study is to identify growth factors that may regulate ACC proliferation, using two human ACC cell lines, the SW13 and the NCI-H295 cells. Our data show that epidermal growth factor (EGF) and transforming growth factor (TGF)-α enhance SW13 cell proliferation and reduced apoptosis, while had modest effects on NCI-H295 cells. Sunitinib, an EGFR receptor (EGFR) inhibitor, and NVP-BEZ235, a PI3K/mTOR inhibitor, reduced cell viability in both cell lines, being counteracted by both EGF and TGF-α in SW13 cells. Since in other settings EGFR regulates cell proliferation by inducing VEGF, we investigated VEGF secretion by the two cell lines. EGF and TGF-α enhanced VEGF secretion only in SW13 cells while had no effects on NCI-H295 cells. In addition, a VEGF receptor blocking antibody significantly reduced EGFR and TGF-α induced cell proliferation.

We investigated in both cell lines the expression of EGFR, which is higher and ubiquitous in SW13 cells, while it is weaker and sparse in NCI-H295 cells, where it is present only on the membrane. These data demonstrate that EGF and TGF-α are important in regulating SW13 cell proliferation, also by modulating VEGF secretion. In conclusion our data suggest that EGFR pathway could represent a new molecular target in drug design for treatment of ACC that display enhanced EGFR expression.

DOI: 10.1530/endoabs.32.P6

P7
Human leukocyte antigen (HLA) and 21-hydroxylase antibodies determine the thyroid peroxidase antibody status of patients in autoimmune Addison’s disease
Marissa Penna-Martinez1, Julia M. Schwartz1, Faroqui Shaghbi2, Gesine Meyer2, Anette B. Wolff2, Stephanie Halime3, Holger Willenberg4, Nicole Reisch5, Marcus Quinkler6, Christin Seidl7, Eystein Husebye2 & Klaus Badenhoop1
1Division of Endocrinology, Department of Internal Medicine, University Hospital, Frankfurt, Main, Germany; 2Institute of Medicine, University of Bergen, Bergen, Norway; 3Division of Endocrinology and Diabetes, Department of Internal Medicine, University Hospital Wuerzburg, Wuerzburg, Germany; 4Department of Endocrinology, Diabetes and Rheumatology, University Hospital Dusseldorf, Dusseldorf, Germany; 5Division of Endocrinology and Diabetes, Department of Internal Medicine, University Hospital Munich, Munich, Germany; 6Department of Transplantation Immunology, Red Cross Blood Donor Service, Institute of Transfusion Medicine and Immunohematology, Frankfurt, Main, Germany; 7Clinical Endocrinology, Charite Center Campus, Berlin, Germany.

The cortisol secretion level of adrenocortical adenomas range from hormonally silent to overt hypercortisolism. The mechanisms leading to the autonomous hypersecretion of cortisol are unknown. The aim was to identify the gene expression alterations associated with the autonomous and excessive cortisol secretion of adrenocortical adenomas.

Methods
The transcriptome of 22 unilateral adrenocortical adenomas (5 non-secreting, 6 subclinical cortisol-producing, and 11 cortisol-producing) was studied and correlated with cortisol secretion. Among them, the cAMP/PKA pathway seem altered in cortisol secreting adenomas. The PKA-activity/cAMP ratio was increased in adenomas with high PDE8B levels, suggesting that the PDE8B increase is a counter-regulation to limit downstream activation of the pathway.

Conclusion
The transcriptome of adrenocortical adenomas shows a major association with cortisol secretion and identifies specific groups of genes implicated in steroid secretion. Among them, the cAMP/PKA pathway seemed altered in cortisol secreting adenomas.

DOI: 10.1530/endoabs.32.P5
Autoimmune Addison’s disease (AAD) results from the immune mediated selective destruction of adrenal steroid hormone-secreting cells. Autoantibodies (Abs) against 21-hydroxylase (21OH) are diagnostic present in 85–90% newly diagnosed patients. Its genetic susceptibility is conferred by human leukocyte antigen (HLA) DQ and DQ8. In many patients autoimmune disease extends forming the autoimmune polyglandular syndrome type 2 (APS-2). The aim of this study was to test, whether specific HLA alleles in combination with the 21OHAb status were associated with thyroid autoimmunity as detected by thyroid peroxidase autoantibodies (TPO-Abs) in patients with AAD. Patients with AAD (n = 194) were genotyped for HLA and TPO-Abs were measured using an enzyme-linked immunosorbent assay, 21OH-Abs with an in vitro transcription/translation method. The titers of Abs were quantified and defined as positive (pos) or negative (neg) (21OHAb >48 c-index; TPOAb >100 <U/ml). Statistical analysis used Kruskal-Wallis and Spearman’s correlation tests.

HLA high risk (R) alleles (DQ2 and/or DQ8), 21OHAb<pos and TPOAb<pos were present in 71, 86 and 36% of the AAD patients, respectively. Furthermore, in order to evaluate the effect of HLA-21OHAb status on the production of TPO-Abs the patients were divided into four subgroups (Gr): Gr1: HLA<pos, 21OHAb<pos; Gr 2: HLA<pos, 21OHAb<pos; Gr 3: HLA<pos, 21OHAb<pos; Gr 4: HLA<pos, 21OHAb<pos. While the Gr 2 and Gr 4 had significantly higher concentration of TPO-Abs in median (44.5 and 55 U/ml) than Gr 3 (1.3 U/ml; P<0.01). The median of BMI (24.8 kg/m²) and TPOAb was (170 u/l). No correlation was observed between treatment A vs B regarding; BMI (24.8 vs 25.0; P=0.2), waist–hip ratio (0.84 vs 0.85; P=0.5), systolic blood pressure (115.9 vs 114±12.7; P=0.67), nor in insulin sensitivity (8.1±3.6 vs 7.5±2.7 mg/kg per min; P=0.59) but there was a significant difference in diastolic blood pressure (77.2±5.2 vs 72.4±5.5 mmHg; P=0.02).

Conclusion

This is the first study to compare insulin sensitivity in patients with AAD on CSHI vs oral hydrocortisone. CSHI replacement was not superior in terms of insulin sensitivity compared to conventional oral glucocorticoid replacement. Reference


P9

Insulin sensitivity in patients with Addison’s disease: a randomised cross-over trial comparing conventional glucocorticoid replacement therapy with continuous subcutaneous hydrocortisone infusion therapy.


1Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden; 2Karolinska Institutet, Södersjukhuset, Stockholm, Sweden, 3Department of Medical Sciences, Uppsala University, Uppsala, Sweden; 4Institute of Medicine, Haukeland University Hospital, Bergen, Norway.

Background

Conventional glucocorticoid replacement therapies result in unphysiological variation in plasma cortisol levels; concern has been raised regarding long-term metabolic consequences. Glucocorticoid replacement is technically feasible by continuous subcutaneous hydrocortisone infusion (CSHI), which can mimic the normal diurnal cortisol rhythm. The aim of this study was to compare insulin sensitivity in patients with Addison’s disease (AD) on CSHI vs three daily doses (t.d.d.) of oral hydrocortisone.

Design, subjects, and measurements

This was an open randomised, cross-over trial, comparing 2 months of CSHI vs t.i.d. oral hydrocortisone with a minimum of 3 months wash-out period in patients with long duration of AD. Treatment A was oral hydrocortisone with weight-adjusted doses as suggested by Mah et al. (1). Treatment B was CSHI using Solu-Cortef® (50 mg/ml) with a body surface area adjusted dose (10 mg/m² per 24 h). Insulin sensitivity (mg/kg per min) was determined after 2 months of each treatment using the euglycemic hyperinsulimic clamp technique (40 mU/m²).

Whole-body insulin sensitivity (M-value) was calculated from the amount of glucose infused during the last 30 min of the clamp divided by body weight (kg) and period (min) and expressed as mg/kg per min.

Results

Fifteen patients (11 women and 4 men) age (49.4±6.2 years) and AD duration (15.5±10.3 years), took part in the study. After 2 months treatment (cross-over) the mean dose of oral hydrocortisone was (17±2.5 mg) and Solu-Cortef® in CSHI was (19.6±5.5 mg) respectively. There were no absolute differences between treatment A vs B regarding; BMI (24.8±2.1 vs 25.0±2.1 kg/m²; P=0.74), waist-hip ratio (0.84±0.1 vs 0.85±0.1; P=0.65), systolic blood pressure (115.9±12.7 vs 114±12.0 mmHg; P=0.67), nor in insulin sensitivity (8.1±3.6 vs 7.5±2.7 mg/kg per min; P=0.59) but there was a significant difference in diastolic blood pressure (77.2±5.2 vs 72.4±5.5 mmHg; P=0.02).

Conclusion

This is the first study to compare insulin sensitivity in patients with AD on CSHI vs oral hydrocortisone. CSHI replacement was not superior in terms of insulin sensitivity compared to conventional oral glucocorticoid replacement.

Reference


P10

First phase insulin secretion is impaired by aldosterone excess in primary aldosteronism.

Evelyn Fischer, Christian Adolf, Anna Pallauf, Cornelia Then, Martin Bidlingmaier, Felix Beuschlein, Jochen Seissler & Martin Reincke Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, Munich, Germany.

Context

Primary aldosteronism (PA) represents the most frequent cause of a curable secondary arterial hypertension. Conflicting data have been published regarding the effect of aldosterone excess on glucose and lipid metabolism.

Objective

Our aim was to analyze insulin sensitivity and beta cell function in a cohort of PA patients. Prospective follow-up investigations were performed in a subgroup of patients before and after adrenalectomy to assess the metabolic outcome.

Design

Oral glucose tolerance test, combined intravenous glucose tolerance test (ivGTT) - hyperinsulinemic-euglycaemic glucose clamp test and arginine test were carried out after a 12-h fasting period.

Patients

Twenty two consecutive PA patients with both unilateral (n = 14) and bilateral (n = 8) disease were recruited through the Munich center of the German Conn’s Registry. The total group of EH patients (n = 11) of corresponding age, gender

Endocrine Abstracts (2013) Vol 32
and BMI were recruited from our hypertension unit. A normotensive cohort (n = 11) was recruited as control group.

Results
At baseline, first phase insulin reaction in ivGTT was significantly reduced in patients with PA as compared to normal controls (36.0 (24.0; 58.7) vs 90.1 (52.6; 143.8) μU/mL, P = 0.031) and lower in comparison to EH without reaching statistical significance (53.2 (30.8; 73.3) μU/mL, P = 0.125). The study was repeated 6 months after unilatera adrenalectomy in 9 consecutive patients with APA. At this time point, blood pressure was normalized in the majority of patients while BMI remained unchanged (26.9 (25.5; 37.6) vs 27.5 (25.1; 35.6) kg/m², P(=0.401). The first phase insulin reaction in response to glucose significantly increased at follow-up (from 36.0 (25.5; 58.7) to 48.5 (30.4; 95.2) μU/mL, P = 0.038). In contrast, insulin sensitivity, insulin resistance and response to iv arginine did not differ before and after adrenalectomy.

Conclusion
These findings provide evidence that aldosterone excess has a direct negative effect on beta cell function in patients with PA. Accordingly, following adrenalectomy, early insulin secretion improves significantly in these patients.

DOI: 10.1530/endoabs.32.P10

---

**P11**

**Molecular screening for personalized treatment approach in advanced adrenocortical cancer**

Maria Cristina De Martino 1, Abir Al Ghuzlan 2, Christine Do Cao 3, Guillaume Assié 4, Jean-Yves Scaccez 5, Sophie Lebouilleux 6, Sebastien Aubert 7, Rossella Libè 8, Cécile Nozières 9, François Pattou 10, François Borzon-Chazot 11, Rosario Pivonello 12, Clement Mazoyer 13, Jerome Bertherat 14, Martin Schlimburger 15, Ludovic Lacroux 16 & Eric Baudin 17

1Department of Nuclear Medicine and Endocrine Oncology, Institut Gustave Roussy, Villejuif, France; 2Department of Pathology, Institut Gustave Roussy, Villejuif, France; 3Hôpital C. Huriez, CHRU de Lille, Lille, France; 4Hôpital Cochin, Paris, France; 5Hôpital Édouard Herriot, Lyon, France; 6Department of Molecular and Clinical Endocrinology and Oncology, Federico II University, Naples, Italy; 7Translational Research Laboratory, Institut Gustave Roussy, Villejuif, France.

Propose
To screen for the presence of putative targets for new treatments in a large cohort of advanced adrenocortical cancer (ACC) patients.

Experimental design
In 40 adult stage III-IV ACC primary samples, we used comparative genomic hybridization (CGH) and hotspot gene sequencing (with Ion Torrent) to describe the presence of copy number abnormalities and mutations in more than 40 genes involved in cancer development and putative drug sensitivity (HER2; EGFR; BRAF; KRAS; PIK3CA etc.).

Results
The most frequent copy number alteration observed was the deletion of the tumor suppressor genes CDKN2A (four cases of 28 that generate informative profiles; 14.3%) and CDKN2B (3/28 cases 10.7%) both located in the region Chr9p21. Lower level loss of the region Chr9p21 were also frequently observed (7/28 cases 25%). The most frequent mutations were in the genes of TP53, ATM and CTNNB1 (6, 5, and 4 cases 15, 12.5, and 10%). Amplifications of FGFR1, FGF9, and FR32 have been seen in three different subjects 7.5%. Other abnormalities were detected in single patients (BRCA1, PSM3; RPTOR; MYC; ABL1; PTK2; FLT3, MDM2; ERBB4; SMO; STK11; and GNAS). Same recurrent association of abnormalities were: deletion of CDKN2A and ATM mutation; TP53 and CTNNB1 mutation.

Conclusions
Drugs targeting cell cycle could represent nowadays the most relevant new therapeutic approach for patients with advanced ACC. FGFRs pathway could be a potential target for treatment in a subset of ACC patients, while treatment with other targeted therapies could have a rational, based on the genomic alterations, only in selected patients.

DOI: 10.1530/endoabs.32.P11

---

**P12**

**Detection of circulating tumor cells in adrenocortical carcinoma: a monocentric preliminary study**

Giada Poli, Pamela Pinzani, Cristina Scatena, Francesca Salvianti, Elisa Corsini, Letizia Canu, Valentina Piccini, Gabriella Nesi, Massimo Mannelli & Michaela Luconi

University of Florence, Florence, Italy.

Objective
Adrenocortical carcinoma (ACC) is a rare malignancy, whose prognosis is mainly dependent on the stage at diagnosis. The identification of disease-associated markers representing solid biomarkers for early diagnosis and drug monitoring is mandatory to improve survival rate and life quality of patients. CTC are tumor cells originating from primary tumor or metastases. The tumor-induced angiogenesis and invasion allow aggressive tumors to release CTC into blood stream before any detectable metastases are established. Therefore, CTC detection may have enormous potential of assisting malignancy diagnosis, estimating prognosis and monitoring the disease. The presence of CTC in ACC patients has never been investigated so far.

Design and methods
CTC analysis was performed in 14 ACC and 10 adrenocortical adenoma (ACA) patients. Blood samples obtained before (n = 3 patients) and after (n = 10 patients) surgery were filtered on ScreenCell devices (ScreenCell®, polycarbonate membranes with 8 μm pores which isolate CTC on size-base.

Results
CTC were isolated in all ACC but not in ACA samples. Immunochemistry on CTC, compared to the primary tumors, revealed positivity for adrenocortical markers, confirming the adrenocortical origin. When ACC patients were stratified in two classes according to the cut-off of the median value of the clinical parameters (tumor diameter, Ki67, and Weiss) or to the presence/absence of metastasis, a statistical significant difference was found in the number of CTC post-surgery only when diameter (CTC/mL mean ± s.d.: 2.70 ± 3.70 vs 0.59 ± 0.67, P = 0.028 for diameter ≥ 8 cm and < < 8 cm respectively) and metastatic stage (CTC/mL mean ± s.d.: 3.91 ± 4.83 vs 0.70 ± 0.70, P = 0.031, for stage = 4 vs the others respectively) were considered.

Conclusions
Our findings provide the first evidence that circulating tumor cells (CTC) may represent a valid and useful marker to support diagnosis in adrenocortical tumor pathologies. Moreover, CTC seem to correlate with some clinical parameters. Although very preliminary, these results, which need confirmation in a larger series, suggest a potential use of this so called ‘liquid biopsy’ for prognosis and for non-invasive monitoring progression and response to treatments.

DOI: 10.1530/endoabs.32.P13

---

**P13**

**New diagnostic methods for primary aldosteronism with specific antibodies**

Cristina Volpe 1,2, Anders Höög 3,4, Tadashi Ogishima 5, Kuniaki Mukai 6, Beril Hamberger 7 & Marja Thoren 1

1Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden; 2Division of Endocrinology, Department of Internal Medicine, Södersjukhuset, Stockholm, Sweden; 3Department of Oncology and Pathology, Karolinska Institutet, Stockholm, Sweden; 4Department of Clinical Pathology and Cytology, Karolinska University Hospital, Solna, Stockholm, Sweden; 5Department of Chemistry, Faculty of Sciences, Kyushu University, Fukuoka, Japan; 6Department of Biochemistry, School of Medicine, Keio University, Tokyo, Japan; 7Department of Breast and Endocrine Surgery, Karolinska University Hospital, Solna, Stockholm, Sweden.

Endocrine Abstracts (2013) Vol 32

Abstract withdrawn.

DOI: 10.1530/endoabs.32.P12
Background
Among patients diagnosed with primary aldosteronism (PA) due to an aldosterone producing adenoma (APA), about 10% fail to normalize aldosterone hypersecretion after unilateral adrenalectomy, and may instead have bilateral aldosterone producing hyperplasia. With routine histopathology it may be difficult to distinguish between APA and hyperplasia. We have recently reported the use of specific antibodies to identify the source of aldosterone excess in the removed adrenal (Journal of Clinical Pathology, in press). The clinical utility of the procedure has now been evaluated in an extended patient material.

Material and Methods
Between 1986 and 2010, 121 patients underwent adrenalectomy for PA. The cure rate was 88% and median follow-up 4 years. Immunohistochemistry with specific antibodies against the steroidogenic enzymes for aldosterone (CYP11B2) and cortisol (CYP11B1) synthesis was performed in addition to routine histopathology in, until now, a subset of 40 adrenals from both cured and uncured patients.

Results
With immunohistochemistry, the cured patients had typically positive staining for aldosterone synthesis in the adrenal, but not in cortical nodules. Interestingly, in two patients where routine histopathology suggested hyperplasia, it was possible to diagnose an APA as only one nodule showed immunoreactivity for aldosterone. Rarely, cured patients showed nodular hyperplasia, staining positively for aldosterone, which may represent unilateral or bilateral disease. Uncured patients showed nodular hyperplasia with positive staining for aldosterone synthesis. Three assumed APAs stained negatively for aldosterone production but positively for cortisol synthesis.

Discussion
Immunohistochemistry can help to localize aldosterone hypersecretion. This is important for the postoperative follow up as APAs are usually cured, while patients with hyperplasia need long term follow-up due to risk of recurrence.

Conclusions
Immunostaining with antibodies against CYP11B2 and CYP11B1 provides important information about the origin of aldosterone hypersecretion. If our results are confirmed, routine use of immunohistochemistry should be recommended.

DOI: 10.1530/endoabs.32.P14

P15
In vivo and in vitro evidence supporting SSTR/mTOR pathway targeting in adrenocortical cancer
Antonina Germano, Ida Rapa, Eleonora Duregon, Arianna Votta, Arianna Ardito, Marco Volante, Mauro Papotti & Massimo Terzolo
University of Turin, Turin, Italy.

Objective
In vitro data suggest that somatostatin receptors (SSTR) and mTOR pathways might represent reasonable targets for novel therapies, since are involved in growth of adrenocortical carcinoma (ACC). However, in vitro analysis of combination treatments, targeting both mTOR and SSTR as compared to mitotane, and detailed tissue typing mTOR/SSTR pathway are poorly explored in ACC.

Methods
This study was designed to characterize the tissue expression of mTOR/SSTR pathway-related molecules in a series of ACC and to investigate in vitro the effects on growth of SOM230, everolimus and mitotane in ACC cells.

Results
Immunohistochemistry for mTOR-related molecules and SSTR subtypes 1 to 5 was performed on a series of 58 ACC and correlated with clinical characteristics. H295R and SW13 ACC cells were incubated with mitotane, SOM230 and everolimus, either alone or in combination. Cell viability was determined by WST-1 method, and drug interactions were calculated using the combination index (CI). Modulation of mTOR and SSTR 1–5 genes was evaluated under treatments using real time PCR.

Conclusions
Heterogeneous profiles of mTOR-related molecules and SSTR expression was observed in ACC samples, with no significant correlations among the different molecules investigated nor with clinical or pathological parameters. In vitro, everolimus determined cytotoxic effects in both ACC cells, with a synergistic effect combining everolimus with either mitotane or SOM230 and with no significant modulation of mTOR gene. By contrast, SOM230 was not effective when used alone in either H295R or SW13 cells, while in combination with mitotane showed an antagonistic effect in SW-13 cells and a synergistic effect in H295R cells (in these latter cells with a significant up-regulation of SSTR genes).

DOI: 10.1530/endoabs.32.P15

P16
Mortality in long-term follow-up patients with progressively increased patterns of subclinical cortisol hypersecretion
Guido Di Dalmazi, Valentina Vicennati, Alexandre Paccapelo, Uberto Pagotto & Renato Pacifici
Endocrinology Unit, Department of Medical and Surgical Sciences, University of Bologna, Š. Orosi-Malpighi Hospital, Bologna, Italy.

Background
Subclinical Cushing’s syndrome (SCS) is defined as alterations in hypothalamic-pituitary-adrenal axis without classic signs or symptoms of glucocorticoid excess. This condition has been associated to increased risk of adverse metabolic and cardiovascular outcomes, independently of other potential risk factors. However, is still not known if this condition could lead to a higher mortality respect to non-secreting adrenal masses (NSA).

Aim
To evaluate the overall mortality of long-term follow-up patients with NSA, intermediate phenotypes of subclinical hypercortisolism (minor–ImP and major–IMP), and SCS.

Methods
This study involved 167 subjects. None of the patients underwent to surgical treatment of the adrenal mass. According to our previous study, the l-methadexemethasone suppression test (DST) was used as primary diagnostic tool, and patients were classified as below: 110 were defined NSA and 4 SCS, using the most stringent cut-off values (< 50 nmol/l and > 138 nmol/l, respectively). Of the 53 patients with cortisol post-DST between 50 and 138 nmol/l, 29 were defined ImP and 24 IMP, using plasma ACTH and/or urinary free cortisol as additional diagnostic tools. Mean duration of follow-up was 8.8 years.

Results
Patients age was different in the four groups (P = 0.001). Mortality analysis was then performed by Cox regression, using age as covariate. The overall unadjusted hazard ratios were 2.80, 3.82, and 7.70 in ImP (P = 0.015), IMP (P = 0.003), and SCS (P = 0.008), respectively. The hazard ratios adjusted for age were 3.22 and 5.33 in IMP (P = 0.010) and SCS (P = 0.026), respectively, when compared to the NSA group. No significance was found for ImP patients after adjustment for age.

Conclusion
Increasing patterns of subclinical cortisol hypersecretion are associated with increased overall mortality, independently of the effect of age. Further analysis are needed to increase the study population with data from medium-term follow-up.

DOI: 10.1530/endoabs.32.P16

P17
Role of adrenal vein sampling in primary aldosteronism: impact of different diagnostic criteria on subtype diagnosis
Maria-Verena Cicala1, Monica Salvà1, Diego Miotti1, Beatrice Rubin1, Raffaele Pezzani1, Anna Fatalamo1, Maurizio Iacobone1, Barbara Martiacciolo1 & Franco Mentore1
1Endocrinology Unit, Department of Medicine, University of Padua, Padua, Italy; 2Endocrine Surgery Unit, Department of Surgery, University of Padua, Padua, Italy; 3Institute of Radiology, University of Padua, Padua, Italy.

In patients with primary aldosteronism (PA), adrenal vein sampling (AVS) is considered the gold standard to distinguish between unilateral and bilateral autonomous production of aldosterone, while diagnostic imaging tests by CT scan or MRI are often inconclusive for the diagnosis. To date agreement is lacking on the best criteria indicating successful cunamulation and lateralization. The aim of the study was to evaluate the impact of different diagnostic criteria for the successful cunamulation and lateralization on subtype diagnosis and to compare the difference of the findings between adrenal CT scan and AVS.

Seventy-four patients with confirmed PA underwent AVS. The different diagnosis of PA subtypes reached using AVS data assessed by more permissive (type 1) and strict (type 2) criteria were compared. All patients performed CT scan before AVS and imaging results were compared with results of AVSs (using both criteria). Using type 1 criteria AVSs were successful in 86% of patients, and in only 64.5% using type 2 criteria. Type 1 criteria led to a higher rate of diagnosis of unilateral PA (85% of successful procedures) than type 2 (75%). There was considerable disparity in the diagnosis reached, with a concordance in only 45% of patients. In conclusion more permissive criteria for successful cunamulation and lateralization on AVS can lead to incorrect diagnosis and accordingly to inappropriate treatment options. In the selected group of patients with successful AVS, CT findings correlated with AVSs findings in 58.5% of patients using type 1 criteria and in 47.5% using type 2 criteria. Finale diagnosis was based on histological results in 36 patients (49%) which underwent adenalecctomy based on AVSs findings. On
the basis of CT findings alone 17% of patients from the first group and 32.5% of patients of the second group probably would have been incorrectly bypassed as candidates for adrenalecctomy. CT scanning lacks sensitivity and specificity and should be followed by AVS, which is the only reliable means of differentiating unilateral from bilateral PA and lateralizing APAs preoperatively. However, there are still controversies to be solved by large prospective studies on the criteria to adopt for defining the most appropriate cut off for both correct cannulation and lateralization.

DOI: 10.1530/endoabs.32.P17

P18

The diagnosis of nonclassical congenital adrenal hyperplasia due to 21 hydroxylase deficiency in woman can be established by genetic testing or urine steroid profile analysis but not by ACTH stimulation test

Urszula Ambroziak1, Anna Kepczynska-Nyk2, Karolina Nowak1, Ewa Maria Malunowicz1, Emilia Morawska1, Michał Kunicki1 & Tomasz Bednarczuk1

1Department of Endocrinology, Warsaw Medical University, Warsaw, Poland; 2Department of Biochemistry and Experimental Medicine, Children’s Memorial Health Institute, Warsaw, Poland; 3Student Endocrine Circle, Warsaw Medical University, Warsaw, Poland; 4Invicta Fertility Clinic, Warsaw, Poland.

Background

ACTH stimulation test is considered the basic diagnostic tool in the diagnosis of nonclassical congenital adrenal hyperplasia due to 21 hydroxylase deficiency (CAH). The cut off of 17OHP stimulation recommended for diagnosis is 10 ng/ml.

Aim

To assess whether the recommended threshold of 17OHP after ACTH stimulation confirms nonclassical CAH among woman with hyperandrogenism and elevated basal 17OHP level.

Material and Methods

Twenty-seven women age 18–38 years with hyperandrogenism and suspicion of nonclassical CAH based on basal 17-OHP level above 1.7 ng/ml. All patients were ACTH stimulation test performed. If the level of 17-OHP stimulation reached 10 ng/ml or more the genetic testing for CYP21A2 mutation and/or urine steroid profile analysis (GSMS) was done to confirm the diagnosis.

Results

The median basal 17-OHP level was 4 ng/ml (1.8–14). The pick median 17-OHP level after ACTH stimulation was 11.29 ng/ml (2.97–30). Among eight patients with 17-OHP stimulation >10 ng/ml (11.26–30) two nonclassical CAH were confirmed (17-OHP basal level was 14 and 13.75 ng/ml after ACTH stimulation 15 and 16 ng/ml respectively). The urine steroid profile analysis in the rest six patients didn’t confirm the diagnosis of nonclassical CAH. Three of them had genetic testing performed and were diagnosed as heterozygotes.

Conclusions

The diagnosis of nonclassical CAH based on threshold 10 ng/ml of 17-OHP stimulation after ACTH can lead to false positive diagnosis of nonclassical CAH and often unnecessary glucocorticoid introduction. The definitive diagnosis can be established based on genetic testing or urine steroid profile.

DOI: 10.1530/endoabs.32.P19

P19

Genetic analysis does not confirm NCCAH in almost half of the women who had received this diagnosis: preliminary results of an audit

Valeria Alcántara1, Diana Tundidor1, Susan Webb2, Gemma Carreras1, Juan Jose Espinos1, Ana Isabel Chico1, Silvia Martínez1, Francisco Blanco1 & Rosa Corcuy1

1Hospital de la Santa Creu I Sant Pau, Barcelona, Spain; 2CIBERER 747, Barcelona, Spain.

Introduction

Non-classical congenital adrenal hyperplasia (NCCAH) due to 21-hydroxylase deficiency is one of the most frequent autosomal recessive diseases. Genetic analysis performed for genetic counselling revealed a miscorrelation with the clinical diagnosis in several patients at our centre.

Aim

Confirm the genetic diagnosis of NCCAH in women attended for this condition.

Materials and methods

Consecutive patients attended at our centre are to be included. So far 26 patients have undergone medical record study collecting clinical, hormonal, and therapeutic information at diagnosis and follow-up into a standardized database. Analysis of the 21-hydroxylase gene has been performed through polymerase chain reaction, sequencing, and family genetic testing when possible.

Statistics

Descriptive analysis; data are expressed as percentages and medians (P25, P75).

Results

84.6% of the patients were index cases. Age at first symptom was 16 years (9.23) and the number of symptoms was 2 (1–3). The most common manifestations were hirsutism (66.7%), oligomenorrhea (50.0%), infertility (15.4%), acne (11.5%), and alopecia (11.5%). At diagnosis, basal 17-hydroxyprogesterone (17OHP) was available in 73% of patients (21.6 nmol/l (6.97, 41)) and ACTH stimulation for 17OHP in 23% (141.9 (52, 175.2)). Genetic analysis revealed that 11.5% of the patients had no mutations, 30.8% were heterozygous for a single mild mutation, 30.7% homozygous for a mild mutation, and 26.9% compound heterozygotes for one mild and one severe mutation. The most common mutation was mild Val281Ile. Globally 42.3% of the patients’ genetic results did not confirm their clinical diagnosis.

Conclusion

In a substantial subset of patients in follow-up for NCCAH, hormonal work-up at diagnosis was inadequate. In almost half of the patients the genotype did not confirm the diagnosis. The diagnosis was confirmed in 81.3% of those with a sufficient hormonal diagnosis and in 20% of those with an insufficient one. These results compel us to reconsider the diagnostic and therapeutic requirements of these patients.

DOI: 10.1530/endoabs.32.P19

P20

Investigation of β-catenin, N-cadherin, and E-cadherin expression in adrenocortical tumors

Beatrice Rubin1, Raffaele Pezzani1, Maria Verena Cicala1, Maurizio Iacobone2, Andrea Olivotto2, Ambrogio Fassina3 & Fireco Manteri1

1Endocrinology Unit, Department of Medicine, University of Padua, Padua, Italy; 2Endocrine Surgery Unit, Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy; 3Surgical Pathology and Cytopathology Unit, Department of Medicine, University of Padua, Padua, Italy.

Background

Adrenocortical tumors (ACT) are classified as adenomas (ACA) or carcinomas (ACC). β-Catenin constitutive activation is a frequent alteration in benign and malignant ACT. E-cadherin was discovered as a protein associated with β-catenin which plays a crucial role in cadherin-mediated cell adhesion. N-cadherin seems to be involved in the development of malignant ACT, but information regarding expression of N-cadherin or E-cadherin in ACT is very limited. Aim

To evaluate the expression of N-cadherin, E-cadherin and β-catenin in ACT and in ACC cell line models (H295R and SW13).

Methods

We analyzed differential expression of β-catenin, N-cadherin and E-cadherin by immunohistochemistry and by quantitative real-time PCR in 71 sporadic ACT. This study included eight normal adrenal cortex samples (NA), 24 ACC, 18 aldosteronomas (APA), 23 cortisol producing adenomas (CPA), and 6 non-secreting incidentalomas (NSA).

Results

Real-time PCR: compared with NA, β-catenin was over-expressed in 50% of ACC (12/24) and 51% of ACA (24/47); N-cadherin was down-regulated in 75% of ACC (18/24) and in 60% of ACA (26/47). IHC: 47% of ACC (7/15) and 33% of ACA (11/33) presented increased cytoplasmic and/or nuclear β-catenin accumulation; furthermore 100% of ACC (15/15) presented down-expression of N-cadherin and 18 of 33 ACA (55%) were down-regulated. We did not find expression of E-cadherin in any ACT.

Interestingly, Spearman analysis showed correlation between β-catenin and N-cadherin expression (ACC vs ACA).

Conclusion

Our preliminary data suggest that β-catenin overexpression together with the aberrant expression of N-cadherin may participate to progression of ACT.
Identification of these and other differentially expressed genes may enhance our understanding of the molecular biology of ACT development, and may contribute in creating new diagnostic and prognostic tools.

DOI: 10.1530/endoabs.32.P20

**P21**

**Bilateral inferior petrosal sinus sampling in cushing’s syndrome: comparison between an old and a new technique in naples experience**

Monica De Leo, Fabio Tortora, Alessia Cozzolino, Chiara Simeoni, Davide Iacuaniello, Aurora Albano, Francesco Briganti, Sossio Cirillo

Section of Endocrinology, Department of Clinical Medicine and Surgery, Naples, Italy; 2Department of Neuroradiology, Second University of Naples, Naples, Italy; 3Neurological Science, Federico II University, Naples, Italy.

Introduction

Bilateral inferior petrosal sinus sampling (BIPSS) is the test that offers the highest diagnostic accuracy in the differential diagnosis between pituitary and ectopic Cushing’s syndrome (CS). The aim of this study was to compare the diagnostic accuracy of BIPSS performed in the last six years, after the change in the technical procedure with that performed in the past period in Naples centre.

Patients and methods

Seventeen patients with CS (14 patients with pituitary and 3 with ectopic CS) followed-up in our institution between 2007 and 2012 were compared with 10 retrospective patients with pituitary-dependent CS subjected to BIPSS. The change in technical procedure was the use of 4-french (instead of 5-french) hydrophilic-coated vertebral catheters introduced into femoral veins using the Seldinger technique.

Results

In the ten historical patients BIPSS yielded 3 (30%) false-negative, together with a discordant result between baseline and post-CRH stimulation in one case, whereas side-to-side (S/S) gradient indicating a correct lateralization in nine patients (90%). In the 17 recent patients, no false-negative or false positive cases were observed, although in one case an IPS/periphery (P) gradient was found only at baseline evaluation. Moreover, a S/S ratio correctly indicated the localization of the lesion in 100% cases. The mean post-CRH IPS/P (P<0.01) gradient was significantly higher in recent than historical patients, although no significant difference was found in mean IPS/P and S/S gradient at baseline evaluation.

Sensitivity, specificity and predictive value of BIPSS in the recent group was of 100%, whereas sensitivity and positive predictive values were 70 and 100% in the historical group.

Conclusions

In Naples experience the diagnostic value of BIPSS has been improved in the last years likely due to the introduction of new catheters, permitting to reach a diagnostic accuracy and a predictivity of 100% cases.

DOI: 10.1530/endoabs.32.P21

**P22**

**21-hydroxylase and interferon omega autoantibodies in Turner syndrome**

Line Cleemann, Bergitte Oftedal, Christian Trolle, Kirsten Holm, Eystein Husebye, & Claus Gravholt

1Hilleroed Hospital, Hilleroed, Denmark; 2University of Bergen, Bergen, Norway; 3Aarhus Universitet Hospital, Aarhus, Denmark.

Introduction

An increased frequency of autoimmune diseases and an elevated incidence of autoantibodies have been observed in Turner syndrome (TS), but indirect immunofluorescence (IF) has not been able to demonstrate autoantibodies against the adrenal cortex. We asked if the more sensitive radioimmunossorbant assay employing recombinant human 21-hydroxylase was able to identify autoantibodies against 21-hydroxylase, (21OH-Ab) in TS patients; 21-hydroxylase is the major adrenal cortex autoantigen in patients with autoimmune Addison’s disease. Moreover, TS patients were tested for antibodies against interferon omega (IFNω-Ab), a marker for autoimmune polyendocrine syndrome 1 (APS 1) where autoimmune Addison’s disease is one of the main components.

Methods

Blood samples from 144 karyotyped TS (11–62 years) were assayed 21OH-Ab and IFNω-Ab using in vitro transcribed and translated autoantigen. An index was calculated with a cut-off point of 57 and 200 for 21OH-Ab and IFNω-Ab respectively.

Results

Autoantibodies against 21-hydroxylase with low indices were present in 6 TS patients (4.2%); none had INF-omega autoantibodies. Overall, the TS patients had a mean age of 31.6 years (range 11.2–62.2). 53% (n=77) had the karyotype 45X. Hypothyroidism was recorded in 9% (n=20), coeliac disease in 1.4% (n=2), and type 1 diabetes mellitus in 0.7% (n=1). The six TS patients with 21-hydroxylase antibodies had a mean age of 32.7 years (range 17.7–44.7). Two had the karyotype 45X. One patient had hypothyroidism, but none had clinical apparent Addison’s disease.

Conclusion

21-hydroxylase autoantibodies can be detected by using RIA in some patients with TS. These findings add to previous studies showing a high proportion of TS with an array of different autoimmune antibodies. Whether any of the autoantibody-positive TS patients will eventually develop Addison’s disease remains to be seen.

DOI: 10.1530/endoabs.32.P22

**P23**

**Immunohistochemical markers of adrenal cortical tumors**

Barbara Alitieri, Guido Fadda, Anna Capozzi, Alfredo Pontecorvi & Silvia Della Casa

1Endocrinology and Metabolic Disease, Catholic university of Sacred Heart, Rome, Italy; 2Division of Anatomic Pathology and Histology, Catholic University of Sacred Heart, Rome, Italy.

Introduction

Adrenocortical tumors (ACTs) are usually divided in adenoma (ACA) or carcinoma (ACC) according to histopathologic methods. Some lesions are occasionally difficult to classify according to these criteria. We studied the use of some immunohistochemical markers to recognise the difference between malignant and benign tumors.

Materials and methods

We studied 12 patients affected by ACC and 10 by ACA. Clinical evaluation and hormone analysis were performed in all patients who underwent to adrenalectomy. Immunohistochemistry was performed on adrenal tumours tissue except for a singular case in which materials come from lymph node metastasis. We analysed Ki-67, IGF2, Ghrelin, PPARγ, and ACTH expression.

Results

All ten ACAs showed a low Ki-67 <5%, while 4 out of 12 (33%) ACCs showed a high proliferative index (Ki-67 >5%). The Wilcoxon–Mann-Whitney U test demonstrated difference between ACAs and ACCs for Ki-67 (P>0.025). We didn’t find statistically significant differences between IGF2 (P>0.0462), Ghrelin (P=0.738), PPARγ (P<0.403), and ACTH (P<0.369). Although there were not differences for IGF2 between the two groups, we observed an overexpression of this marker in 50% of ACC (IGF2>60%). Analysis based on Spearman correlation didn’t find correlation between stage disease, tumor dimension and immunohistochemical markers in ACCs.

Conclusion

According to the literature, we found Ki-67 could be an useful to distinguish between ACAs and ACCs. Although many studies considered IGF2 as a malignant parameter, our results didn’t confirm its use alone could be helpful to identify malignant lesions. Besides we showed the other different immunohistochemical markers, less commonly investigated in these tumors, should not be useful to discriminate adenoma from carcinoma. None immunohistochemical marker considered in our study showed a correlation with the characteristics of size or local extension of lesions. Therefore, we need more studies about a higher number of patients to obtain much more significant data about IHC utility.

DOI: 10.1530/endoabs.32.P23
P25
Management of Addison’s disease patients using dual release hydrocortisone during periods of intercurrent illness
Ulrika SH Simonsson1, Staniko Skrljević2, Hans Lennermäki3, Claudio Marelli4 & Gudmundur Johannsson5
1Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden; 2Department of Clinical Pharmacology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; 3Department of Pharmacy, Uppsala University, Uppsala, Sweden; 4ViroPharma SRL, Maidenhead, UK; 5Department of Endocrinology, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden.

Introduction
Current management of intercurrent illness (ICI) in adrenal insufficiency (AI) is inadequate. We attempted to optimise ICI regimens with pharmacokinetic simulations of a dual-release (DR) hydrocortisone (HC) and tested them in a formal clinical trial.

Methods
This work consisted of: i) dosing recommendations in episodes of mild ICI with DR-HC using simulations with a population pharmacokinetic model, ii) collection of ICI episodes with increased cortisol use and outcome assessment using quality-of-life (QoL; Fatigue Impact Scale, Short-Form 36), and iii) exposure-response model for probability of developing an ICI based on logistic regression.

Data was collected from a 3-month cross-over trial comparing once-daily DR-HC with immediate-release (IR) HC given TID using the same daily dose of HC. Further safety data for DR-HC were available for 80 patients over 27 months.

Results
Cortisol profiles were obtained in 62 patients after administration of DR-HC on 116 occasions, and in 16 healthy volunteers. Simulations showed that an additional DR-HC dose at 8 ± 2 h after the morning dose or TID with 8 h intervals provided greater 24 h coverage IR-HC TID.

There was no difference in ICI episodes between DR-HC and IR-HC in mean percentage of days with extra doses, 2.5 and 1.6% respectively (median both 0.0). QoL after an ICI episode was not different between DR-HC and IR-HC. The total experience with DR-HC in mild ICI corresponded to 145 patient years (293 episodes).

There was no correlation between total HC exposure (AUC 0–24 h) and numbers of AEs. The estimated probability of at least one adverse event episode was not associated with total (AUC 0–24 h) HC exposure; DR-HC (P = 0.64) and IR-HC (TID) (P = 0.52).

Conclusions
In this first prospective study in ICI, the suggested DR-HC regimens were successfully implemented in the clinical management of AI patients. Simulations suggested DR-HC regimens gave greater coverage over 24 h than IR-HC.

DOI: 10.1530/endoabs.32.P25

P26
Longitudinal assessment of adrenocortical responses to low-dose ACTH in critically ill septic patients
Dimitra A Vassiliadis1, Ioanna Dimopoulou2, Maria Zervou2, Marina Tzanela2, Hercules Tsgaris7, Callirrhoe Augustatou8, Evangelia Douka7, Olga Livaditi2, Stylianos Orfanos1, Anastasia Kotanidou8, Apostolos Armaganidis2 & Stylianos Tsagarakis1
1Department of Endocrinology, Diabetes and Metabolism, Evangelismos Hospital, Athens, Greece; 2Department of Critical Care Medicine, Medical School, Evangelismos Hospital, National and Kapodistrian University of Athens, Athens, Greece; ‘Attiko’ University General Hospital, University of Athens, Greece, Athens, Greece.

Introduction
The hypothalamo-pituitary adrenal axis has been extensively investigated in sepsis. Most studies concentrated in the acute phase and in most the high-dose ACTH stimulation test has been applied. Studies extending in the post-acute phase by using the more physiological low-dose ACTH stimulation are scarce. We aimed to investigate the time course of cortisol levels before and after stimulation with 1μg Synacthen in mechanically ventilated septic patients, over a 30-day period.

Methods/design
We studied 51 patients admitted to ICU with sepsis (n = 16), severe sepsis (N = 19), or septic shock (N = 16). Total serum cortisol was measured before and 30 min after the i.v. administration of 1 μg Synacthen upon admission and every 3–4 days thereafter until administration of glucocorticoids (n = 6), death (N = 15), recovery (n = 24) or completion of 30 days (n = 6). Mixed-effect models were used to analyze the time progression of cortisol levels. Patients who received glucocorticoids were excluded from any analysis referring to survival.

Results
Administration of 1 μg Synacthen significantly increased cortisol levels at all time points (P < 0.001). In the whole cohort, there was no significant variation in baseline and stimulated cortisol levels during the entire observation period. Throughout the study period patients admitted with septic shock had significantly higher baseline and stimulated cortisol levels compared to those admitted with sepsis or severe sepsis (P < 0.01) and non-survivors had higher baseline cortisol levels compared to survivors (P < 0.01). On admission, stimulated cortisol levels were similar between survivors and non-survivors but the difference between stimulated and baseline cortisol (ΔF) was lower in non-survivors. Subsequently, non-survivors had higher stimulated cortisol levels compared to survivors (P < 0.001) with no difference in ΔF.

Conclusion
Baseline and stimulated cortisol levels remain relatively unchanged during the process of sepsis. Patients admitted with septic shock had higher baseline and stimulated cortisol levels, reflecting the severity of sepsis. Higher cortisol levels were associated with increased mortality.

DOI: 10.1530/endoabs.32.P26

P27
Increasing prevalence of Addison’s disease in Germany: health insurance data 2007–2011
Gesine Meyer1, Kathrin Neumann2, Klaus Badenhoop1 & Roland Linder2
1Division of Endocrinology, Department of Medicine 1, University Hospital Frankfurt, Frankfurt A.M., Germany; 2WINEG-Scientific Institute of the TK for Utility and Efficiency in Health Care, Hamburg, Germany.

There are no epidemiological data of Addison’s disease in Germany. Since there is no national registry for this rare disease alternative data sources need to be retrieved. The Technikerkrankenkasse (TK) is one of the large German health care insurance providers covering nearly 10% of the population. Documentation of diagnoses by all members with a doctor contact is evaluated by a scientific institute (WINEG). Screening of the database for Addison’s disease was designed to filter out all causes of secondary, iatrogenic, traumatic or other non-idiopathic forms of primary adrenal failure. The prevalence of Addison’s disease was found to range between 100 and 129 per million and showed a steady increase over the five years 2007–2011 of 22.5%. The prevalence was lower in men (73–90 per million, increase 18.9%) than in women (129–169 per million, increase 23.7%). Autoimmune comorbidities were found in 58.4%. Prevalence data for the more frequent autoimmune diseases type 1 diabetes mellitus and vitiligo did not change significantly over the years 2008–2011. These data provide a first epidemiological profile of this rare endocrine disease in Germany. Although the prevalence of Addison’s disease appears slightly lower than in the Scandinavian countries, the increasing figures particularly in females warrant further investigation into causes and triggers of autoimmune adrenal destruction. Hereby we can show that health insurance data provide a valuable tool for epidemiological studies in the absence of national registries and allow providers to improve resource allocation and management of rare and also more common chronic diseases.

DOI: 10.1530/endoabs.32.P27
15th European Congress of Endocrinology 2013

P28
The role of late-night salivary cortisol measurement in the diagnosis of subclinical hypercortisolism in patients with adrenal incidentalomas
I Perogamvros, M Tzanela, A Kolleti, S Tairona, E Memi & S Tsagarakis
Department of Endocrinology, Diabetes and Metabolism, Evangelismos Hospital, Athens, Greece.

The diagnosis of subclinical hypercortisolism (SH) is a challenging issue, especially as the high prevalence of adrenal incidentalomas (AI) is increasingly recognized. The diagnosis of subclinical hypercortisolism relies on a combination of tests that include overnight (ODST) low dose dexamethasone suppression (LD DST), plasma ACTH, and 24-h urinary free cortisol ( UFC). Late night salivary cortisol (LNSC) has been successfully used in the diagnosis of Cushing’s syndrome (CS) and is now considered a first-line screening test. Nevertheless, its use in SH has been evaluated only in a limited number of reports. Therefore, we tested whether measurement of LNSC can be used to screen patients with AI for SH.

Thirty-five patients (21 females) were studied; six patients had CS (group A); and 29 patients had AI. Based on published diagnostic criteria for SH (post-LDST cortisol levels >1.8 μg/dl and at least one of the following: ACTH levels <10 pg/ml and high UFC >120 μg/24 h, corresponding to the upper normal limit of our assay) patients with AI were divided in two groups: patients with SH (group B, n = 10) and patients without SH (group C, n = 19). Results were compared to normal controls (group D, n = 14). LNSC was measured at 23:00 on the day of the study.

LNSC levels (μg/dl) were higher (P < 0.05) in groups A (0.79 ± 0.36) and B (0.21 ± 0.06) compared to groups C (0.06 ± 0.01) and D (0.03 ± 0.01). ROC curve analysis revealed that SH can be diagnosed with the sole measurement of late-night salivary cortisol with 100% sensitivity but 50% specificity, with a cut-off of 0.045 μg/dl (AUC = 0.95; 95% CI: 0.79–1.03, P = 0.0008). A higher cut-off of 0.055 μg/dl diagnosed SH with 90% sensitivity and 71.5% specificity. These data illustrate that late-night salivary cortisol is of value in the diagnosis of SH in patients with AI. Taking into consideration the ease of sampling, we suggest that salivary cortisol may be used as an additional screening test in this patient group.

DOI: 10.1530/endoabs.32.P28

P29
Aldosterone measurement: performances of a new fully automated chemiluminescence-based immunoassay
Damien Gruson & Thibault Lepoutre
Cliniques Universitaires Saint-Luc, Brussels, Belgium.

Introduction
Measurement of aldosterone, the major mineralocorticoid secreted by adrenal cortex, is important for the screening of primary aldosteronism and for the clinical assessment of hypertensive patients. RIA remain widely used for the measurement of aldosterone but some automated immunoassays are emerging.

The aim of our study was to evaluate the performances of a new automated aldosterone immunoassay.

Methods
Method imprecision of the Liaison® aldosterone assay ( Diasorin), a fully automated immunoassay with chemiluminescence based detection, was determined with quality control materials and a pool of serum samples. Method comparison was performed with a commercial RIA ( coat-a-count®, Siemens) in 91 patients samples.

Results
With quality control materials, between-run coefficients of variation (CV) were 8.3% at 4.9 ng/ml (n = 15) and 5.3% at 25.4ng/ml (n = 11) with the Liaison® assay. For the serum pool with a concentration of 16.5 ng/ml, close to our laboratory cut-point of 14 ng/ml, the between-run coefficient of variation was 6.3% (n = 8). A positive and significant correlation was observed between the two methods (r = 0.96, P < 0.001). For samples with aldosterone concentrations below 14 ng/ml (n = 65), Passing and Bablok regression analysis provides a slope of 0.99 and an intercept of 0.02, without significant deviation of linearity. The mean difference observed on the Bland and Altman plot was 0.2 ng/ml. For samples with aldosterone concentrations higher than 14 ng/ml (n = 23), Passing and Bablok regression analysis provides a slope of 1.00 and an intercept of –1.03, without significant deviation of linearity. The mean difference observed on Bland and Altman plot was 1.1 ng/ml.

Conclusions
Our study demonstrated satisfactory precision for the Liaison® aldosterone assay and results comparable to those of the RIA. Therefore, if our preliminary results are confirmed by larger studies, the Liaison® assay might be relevant for screening of primary aldosteronism and for the assessment of hypertensive patients.

DOI: 10.1530/endoabs.32.P29

P30
Patients with Addison’s disease have increased frequency of the metabolic syndrome: a case–control study
Ragnhildur Berthórsdóttir, Öskar Ragnarsson & Gudmundur Johannsson
Department of Endocrinology, Sahlgrenska University Hospital, Gothenburg, Sweden.

Background
Patient’s with Addison’s disease (AD) have increased morbidity and mortality. Cardiovascular disease is considered the leading cause of death. The aim was to study cardiovascular risk factors in patients with AD.

Methods
In a single-centre, case–control study 78 patients (52 women) with AD were compared to 78 controls, matched for gender, age, BMI, and smoking habits. Serum was collected in a fasting state for measurement of lipids and glucose metabolism, supine blood pressure measured and computed tomography used to assess abdominal subcutaneous and visceral fat. The IDF 2006 criteria were used for the classification of the metabolic syndrome (MS).

Results
Patients and controls were well matched with a mean age of 53 years and BMI of 25 kg/m². The mean (s.d.) duration of AD was 17 years (12). The median (range) daily hydrocortisone and fludrocortisone doses were 30 mg (10–50 mg) and 0.1 mg (0–0.2 mg) respectively. Sixteen patients (21%) with a mean age of 59.8 (10.5) years fulfilled the criteria for the MS compared to eight controls (10%, P = 0.09) aged 69.7 (11.6) years.

Fifteen percent of the patients had diabetes mellitus (type 1, 6% and type 2, 9%) and 44% had hypothyroidism compared to 1 and 3% of the controls. More patients had pharmacological treatment for hypertension (22 vs 5%; P = 0.002) and dyslipidemia (14 vs 1%; P = 0.003).

The HOMA-index and the amount of abdominal subcutaneous and visceral fat mass were not different among the groups but triglyceride concentration was increased (P = 0.014), LDL-cholesterol reduced (P = 0.025) and HDL-cholesterol was increased (P = 0.091) in the patients as compared with controls.

Conclusion
Patients with AD receiving standard replacement therapy have higher frequency of MS in a younger age and higher triglycerides compared to well matched controls. This may be explained by the relatively high hydrocortisone dose used for replacement. The control group which might contribute to the increased cardiovascular death previously suggested.

DOI: 10.1530/endoabs.32.P30

P31
Reliability of serum versus salivary cortisol in ACTH test
Mikulas Kosak1, Vaclav Hana1, Martin Hill2, Katerina Simunkova1,2, Zdena Lacinova1, Michal Krsek1 & Josef Marek1
13rd Department of Medicine – Department of Endocrinology and Metabolism, First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Prague, Czech Republic;2Institute of Endocrinology, Prague, Czech Republic.

Introduction
Salivary cortisol measurement, representing free cortisol, seems to be a promising alternative method to serum cortisol. Besides its use in the diagnostics of hypercortisolism, it could be of help in evaluation of adrenocortical reserve. It might be useful especially in patients on estrogen replacement, which modulates transcorin and hence total cortisol levels.

Aims
Compare the reliability of salivary vs. serum cortisol assessment during ACTH test.

Patients
We have performed ACTH test in 84 subjects (mean age 63; 66 men) with clinical suspicion on hypocorticism. According to the peak serum cortisol (≥ 500 nmol/l) patients were divided into two groups. Group A with normal response (n = 76; mean age 64; 60 men) and Group B with hypocorticism (n = 8; mean age 61; 4 men).

Endocrine Abstracts (2013) Vol 32

DOI: 10.1530/endoabs.32.P31
Methods
250 µg teracosactide was injected intravenously. The blood and saliva were obtained before, in 30 and 60 min afterwards.

Results
Medians of serum cortisol in group A were 445; 766 and 902 nmol/l in 0, 30, and 60 min and 256; 394; and 453 in group B respectively. Medians of salivary cortisol were 6.9; 14.5 and 22.5 nmol/l in group A and 3.5; 5.1 and 4.8 nmol/l in group B. There was a significant correlation between serum and salivary cortisol levels during the test. The percent of variability as an expression of discriminating power, explained by the repeated measures ANOVA model, was significantly \((P=0.021)\) higher for serum cortisol \((R^2=93.4\%)\) compared to salivary one \((R^2=89.3\%)\).

Conclusion
Our data show significant correlation between salivary and serum cortisol levels during the ACTH test. Measurement of serum cortisol has superior discriminating power compared to salivary cortisol in standard evaluation of adrenocortical reserve not influenced by estrogen replacement.

**DOI:** 10.1530/endobs.32.P31

---

**P32**

**Diagnostic performance of first line biochemical tests to differentiate ACTH-ectopic syndrome among ACTH dependent Cushing’s syndrome**

Zhanna Belaya, Liudmila Rozhinskaya, Natalia Dragunova, Larisa Dzeranova, Svetlana Arapova, Evgenia Marova, Galina Kolesnikova & Galina Melnichenko

The National Research Center for Endocrinology, Moscow, Russia.

**Introduction**

This study evaluates the diagnostic accuracy of clinical features and first line routine screening tests to differentiate ACTH-ectopic syndrome from Cushing’s disease (CD).

**Materials and methods**

The retrospective clinical and biochemical presentations of 180 patients with histologically proven ACTH-dependent Cushing’s syndrome (CS) (159 CD, 21 ACTH-ectopic syndrome) were compared according to the cause of hypercortisolism. ROC-analysis was performed to estimate the diagnostic accuracy of the first line tests (2300 h serum cortisol, 24 h urinary free cortisol (24 h UFC) and ACTH rhythm in plasma) to differentiate ACTH-ectopic syndrome. A threshold for the test with the highest area under the curves (AUC) was chosen based on the maximum sum of sensitivity and specificity. Serum cortisol and plasma ACTH were assayed by electrochemiluminescence Cobas e601 Roche. 24 h UFC was measured by an immunochromulinescense assay (extraction with diethyl ether) on a Vitros EC1

**Results**

The patients with ACTH-ectopic syndrome (in 15 cases bronchial carcinoid, in four – carcinoid of thyman, in one instance small cell carcinoma of the lung and in one – carcinoid of the appendix) had higher rates of low traumatic fractures (\(P=0.04\)), increased serum late-night cortisol, 24 h UFC, morning and evening ACTH and lower levels of potassium (\(P<0.01\) for all parameters) vs CD. Late-night plasma ACTH showed the highest AUC (0.845 (95% CI 0.764–0.926)) to differentiate ACTH-ectopic syndrome from CD vs morning plasma ACTH – 0.790 (95% CI 0.673–0.908); late-night serum cortisol – 0.754 (95% CI 0.622–0.886) or 24 h UFC 0.619 (95% CI 0.481–0.758). A cut off value of 108.9 pg/ml for late-night ACTH yielded a sensitivity of 70.6% and a specificity of 81.7%.

**Conclusions**

Of all the clinical features and first line tests, the disturbance of the ACTH rhythm and high late-night plasma ACTH values in patients with proven CS is the most suggestive of ACTH-ectopic syndrome.

**DOI:** 10.1530/endobs.32.P32

---

**P33**

**Salivary cortisol is a useful tool to assess the immediate response to pasireotide in patients with Cushing’s disease**

Marina Cardinali1, Laura Trentimoni1, Carolina Concettini1, Giorgia Marcelli1, Barbara Polenta1, Maurizio Spinello2, Marco Boscaro1 & Giorgio Arnaldi1

1Division of Endocrinology, Polytechnic University of Marche Region, Ancona, Italy; 2Novartis Pharma, Origgio, Italy.

**Introduction**

Pasireotide is a promising treatment option for patients with Cushing’s disease (CD). The measurement of salivary cortisol is useful for diagnosing hypercortisolism and monitoring patients with CD following pituitary surgery. It may also be a better index of cortisol secretion than serum cortisol or urinary free cortisol (UFC). We investigated the value of salivary cortisol in monitoring short-term efficacy of pasireotide in patients with CD.

**Methods**

Seven patients (five females, two males; mean age 35.3±7.4 years) received pasireotide 600 µg bid for 15 days in the Phase II study CSOM230B2208. Morning and midnight cortisol, ACTH and morning serum cortisol were assessed at baseline and after 1, 5, 12, and 15 days of treatment. UFC was determined at baseline and day 15.

**Results**

On day 15, morning salivary cortisol had decreased in all patients; overall mean decrease from baseline was 70% (27.7±30.8–8.2±7.7 nmol/l). Mid morning salivary cortisol had decreased in six patients and normalized in two; overall mean reduction from baseline was 50% (27.2±38.6–13.4±15.4 nmol/l). Decreases in morning and midnight salivary cortisol were observed from day 1 (mean reduction from baseline of 34 and 20% respectively) and persisted until day 15; the greatest decrease was on day 5 (mean reduction of 70 and 58%, respectively). At day 15, mean UFC had decreased from baseline by 65% (1711±1941–593±560 mmol/24 h). UFC was normalized in one patient (14%), who also had normalized midnight salivary cortisol, thereby restoring cortisol rhythm. Changes in ACTH and serum cortisol were similar to those of salivary cortisol.

**Conclusions**

Pasireotide rapidly reduced and normalized salivary cortisol. Salivary cortisol may be a simple, non-invasive biomarker to assess immediate response to pasireotide in patients with CD, particularly to determine whether cortisol rhythm is normalized in patients with normalized UFC levels. More studies are necessary to confirm these preliminary results.

**DOI:** 10.1530/endobs.32.P33

---

**P34**

**Male hypogonadism in Addison’s disease – an under-recognized problem**

Ian Ross, Dirk Blom & David Haarburger

University of Cape Town, Cape Town, South Africa.

**Introduction**

Male hypogonadism may complicate Addison’s disease (AD), but the prevalence of testosterone deficiency in adult males with primary hypoadrenalinism is unknown.

**Methods**

Male patients older than 18 years of age enrolled in the South African AD national registry were screened for biochemical testosterone deficiency (early morning basal testosterone <9.9 nmol/l). Testing was also performed to see if these subjects were more susceptible to metabolic disease.

**Results**

Of the 42 males studied, 14 (33%) were hypogonadal (5 previously diagnosed, 9 newly diagnosed). The presence of testosterone deficiency was not related to age, the duration of disease, or the hydrocortisone dose required. Underlying causes of AD for the hypogonadal group were autoimmune in 7 (50%), tuberculosis in 3 (21%), X-linked adrenal hypoplasia in 2 (14%) and 2 (14%) were idiopathic. None of the 14 hypogonadal subjects had anti-gonadal autoantibodies. Untreated hypogonadal subjects had a higher BMI compared to eugonadal subjects (\(P<0.001\)). There was no difference found between the two groups in terms of total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides or fasting glucose. Luteinizing hormone and follicle stimulating hormone did not differ between the groups, however dehydroepiandrosterone sulphate was significantly decreased in the hypogonadal group (0.31 µmol/l vs 0.57 µmol/l, IQR: 0.27–0.37 vs 0.75–1.50, \(P=0.005\)).

**Conclusions**

Biochemical testosterone deficiency was highly prevalent in this AD group and not related to age or duration of AD. Untreated hypogonadal subjects had increased BMI and hCRP, but no difference was found in their lipid profiles, or glucose levels. It may be worthwhile to evaluate all male patients periodically with AD for testosterone deficiency, as testosterone replacement may improve long-term subjective and clinical parameters.

**DOI:** 10.1530/endobs.32.P34
A survey of the prevalence and treatment outcome of active Cushing’s disease in Belgium

Marie Nex, Heidi Nauwelaerts, Guy T Sjoen, Brigitte Velkeniers, Bernard Corvillain, Pascale Abens, Albert Beckers, Christophe De Block & Dominique Maiter

1University Hospitals Leuven, Catholic University of Leuven, Leuven, Belgium; 2Novartis Pharma Belgium, Vilvoorde, Belgium; 3Ghent University Hospital, Gent, Belgium; 4Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Brussels, Belgium; 5Erasmus University Hospital, Université Libre de Bruxelles, Brussels, Belgium; 6St. Augustinus Hospital, Wilrijk, Belgium; 7Centre Hospitalier Universitaire de Liège, University of Liège, Liège, Belgium; 8Antwerp University Hospital, University of Antwerp, Antwerp, Belgium; 9St. Luc University Hospital, Université catholique de Louvain, Brussels, Belgium.

To estimate the point prevalence of active Cushing’s disease (CD) in Belgium, all endocrinologists were invited to perform a retrospective chart review of the CD patients they had been treating between 1-1-2009 and 31-12-2010. Only patients requiring cortisol lowering therapy because of cortisol excess could be included, such as de novo patients (n = 53), previously diagnosed patients with persisting/recurrent disease after pituitary surgery and/or radiotherapy (n = 27) or on primary or no medical therapy (n = 13) and finally patients with previous surgical remission but relapsing in 2009 or 2010 (n = 9). Other CD patients in remission or controlled without cortisol lowering therapy, e.g. those with bilateral adrenalectomy, were excluded.

The mean age at time of diagnosis of these 102 subjects (82% female) was 45 ± 15 yrs. The annual incidence of CD based on the de novo cases in 2009 and 2010 was 2.14 (95%CI: (1.36; 3.21)) and 2.77 (1.87; 3.95) per million inhabitants, respectively.

Over the two years period 57 pituitary surgeries were reported in 53 patients, followed by surgical remission in 79%. Remission rate (combined early remission and delayed control) was 72% in 46 first procedures and 82% in 11 repeat surgeries. At the end of the observation period, 33 of 49 patients diagnosed before 2009 were still active. One had died while 15 were in remission after first (7) or repeat (7) pituitary surgery or after adrenalectomy (1). Of the newly diagnosed patients 30 were in surgical remission (followed pituitary surgery in 26 and adrenalectomy in 4).

After exclusion of another death, 22 new patients still had active CD on 31-12-2010, although in 13 of these, first surgical treatment had yet to be performed. These data result in an estimated point prevalence of active CD on 31-12-2010 of 5.0 per million (95%CI (3.7; 6.5)), based on the entire Belgian population on that date.

This retrospective epidemiological study provides insight in the number of CD patients that might need additional treatment, including steroidogenesis inhibitors or pituitary-targeted drugs, when (repeat) pituitary surgery fails. Could be candidates for treatment with the new pituitary-targeted drug pasireotide.

Audits should describe the patient population, audit methodology, and outcomes which should encompass any change/benefit to clinical practice.

DOI: 10.1530/endoabs.32.P35
adrenal tumour. In all patients were examined plasmatic metanephrines and was
excluded fœochromocytoma before biopsy. All patients were admitted after
endosnographic biopsy to clinical department and were observed till next day.
Results
14 patients, 6 men and 8 women were included in the study. In all patients were
not observed any complication of biopsy. In 5 cases there were bilateral tumours,
in 3 cases right adrenal tumours and in 6 cases left adrenal tumour. 3 tumours
were bigger than 4 cm; others were smaller than 4 cm. In one case of unilateral
tumour no biopsy was performed – adrenal gland was too small for secure biopsy;
in one case of bilateral tumour was performed only one sample from anatomical
reasons. In other cases totally 17 samples were taken; 2 were marginally
sufficient. 15 were sufficient. In 9 cases, two bilateral and 7 unilateral, were
biopsies benign and patients were observed. In 5 cases was indicated unilateral
adrenalectomy. One fœochromocytoma, one metastasis of ovarian carcinoid
tumour, two adenoacarcinoma and one adrenal cortex tumour (borderline
characteristic between carcinoma and adenoma).
Conclusion
Endosnography-guided fine-needle aspiration biopsy seems to be useful and safe
method of differential diagnosis of atypical adrenal tumours. It can reveal any
primary or secondary malignancy in early stage, with good possibility of surgical
treatment.
DOI: 10.1530/endoabs.32.P39

P39
The Urinary Aldosterone in the Diagnosis of Primary Aldosteronism
Miroslav Solar1,2, Eva Malirova1, Marek Ballon1 & Jiri Cerab1,2
1University Hospital Hradec Kralove, Hradec Kralove, Czech Republic;
2Medical Faculty Hradec Kralove, Charles University Prague, Hradec Kralove,
Czech Republic.

Introduction
The estimation of urinary aldosterone is one of the recommended confirmatory
tests when diagnosing primary aldosteronism (PA). The study assessed the
interpretation of the urinary aldosterone secretion (UA).
Subjects and methods:
The study enrolled both healthy volunteers and patients with suspected PA.
Estimation of UA in 24-hour urine specimen was performed in enrolled
individuals. Increased oral salt intake was recommended before and during urine
collection. The data of healthy volunteers were intended to facilitate the
interpretation of the data of patients with suspected PA. In patients with suspected
PA, saline infusion testing (SIT) was performed twice in order to definitely
confirm or exclude PA diagnosis. Both SITs were performed under identical
conditions, i.e. after the drugs interfering with renin-angiotensin-aldosterone
system were withdrawn. The individuals who exhibited discordant SIT results
were excluded from the study.

Results
Based on the data of 30 healthy volunteers, upper UA reference value was
determined: 43 nmol/day when urinary sodium exceeded 200 mmol/day.

Eighty-five urine samples from 45 patients with suspected PA were used to
analyze the UA interpretation. In respect to PA diagnosis based on SIT, UA > 19
nmol/day was characterized by 96% sensitivity and UA > 92 nmol/day was
associated with 96% specificity. Upper reference value based on the data from
healthy volunteers was characterized by 77% sensitivity and 60% specificity.

Conclusions
Urinary aldosterone can reliably confirm or exclude the diagnosis of primary
aldosteronism. However, this approach is applicable only in a limited number of
individuals who exhibit very low or very high urinary aldosterone secretion.
DOI: 10.1530/endoabs.32.P39

P40
Autoimmune polyglandular syndrome on a cohort of patients with primary
adrenocortical insufficiency
Sofia Gouveia, Cristina Ribeiro, Micaia Alves, Joana Saraiva,
Carolina Moreno, Daniela Guello & Francisco Carrilho
Endocrinology, Diabetes and Metabolism Department, Coimbra’s
University Hospital, Coimbra, Portugal.

Introduction
On average, 40 to 50% of the patients with autoimmune adrenocortical
insufficiency will eventually develop an autoimmune polyglandular syndrome
(APS). Our aim was to characterize a population with primary adrenocortical
insufficiency (AI) and determine the prevalence of other autoimmune disorders
that might establish the diagnosis of APS.

Materials and methods
We included patients with primary AI under surveillance at our Department.
Those with iatrogenic causes for AI were excluded. The referred population was
caracterised on what concerns to gender, age, disease’s duration, familial history
of AI and aetiology. We assessed autoimmune markers for Addison disease, type
1 diabetes, gastritis, thyroiditis and celiac disease in those without an obvious
cause for AI. Positive markers triggered evaluation of associated dysfunction.

Results
Thirty patients (63.3% females) were included. Mean age- 46.9 ± 15.9; disease’s
duration- 19.9 ± 12.1 years. Familial history of AI was present in 23.3% of the
cohort. On what concerns to AI aetiology, 63.3% were autoimmune, 20%
congenital adrenal hyperplasia, 6.7% X-linked adrenoleukodystrophy, 3.3%
tuberculosis, 3.3% antiphospholipid antibody syndrome and 3.3% undetermined.

Considering the subgroup of autoimmune AI, 31.5% had at least one positive
diabetes autoantibody (40% already diagnosed as having diabetes), 42.1% displayed
autoimmune gastritis markers (62.5% with hypergastrinemia, 25% iron
deficiency and 12.5% anaemia). Positive thyroid autoantibodies were present in
63.2% of the patients; 75% of them had thyroid dysfunction (hypothyroidism
88.9%). Celiac disease markers were not detected in this population.

Enough criteria for an APS diagnosis were fulfilled in 73.7% patients (85.7% APS
type 2; 14.3% APS type 4).

Conclusion
The main aetiology for AI was autoimmune. The commonest associated
autoimmune disorders were thyroiditis (63.2%) and gastritis (42.1%).

An early identification of other autoimmune disorders in patients with
autoimmune AI will ensure an adequate treatment and follow-up, improving
their quality of life. Therefore, a regular screening for autoimmunity is advisable.
DOI: 10.1530/endoabs.32.P40

P41
Non-classic adrenal hyperplasia (NCAH) in patients with bilateral
adrenal incidentally discovered tumors
Elwira Przybyl-Mazurek, Marta Tracz-Bujnowicz, Sylwia Kuzniarcz-Rymarz
& Alicja Hubalewska-Dydejczyk,
Department of Endocrinology, Jagiellonian University Medical College,
Krakow, Poland.

The prevalence of adrenal incidentalomas in computed tomography (CT) studies
ranges from 0.6–1.9%. Adrenal masses are detected bilaterally in 10–15% of the
cases.

Non-classic adrenal hyperplasia (NCAH), also termed as late onset of CAH, is
a very mild form of 21-hydroxylase deficiency. The incidence of disease is
estimated at 0.1% of population. Reported prevalence in women with androgen
excess range from 0.6 to 9%.

Some patients have an overresponsive glucocorticoid response to ACTH
stimulation, possibly reflective of subtle adrenal hyperplasia.

The aim of the study was to evaluate the prevalence of NCAH among patients
with incidentally discovered bilateral adrenal tumors.

Material and methods
Seventy eight patients, 18 men and 60 women aged from 42 to 74 years with
incidentally discovered in computed tomography (CT) bilateral adrenal
tumors were examined. The diameter of tumors ranged from 17 to 52 millimeter and
features of CT scanning suggested their benign character. Excess of the
glucocorticoids or mineralocorticoids was excluded. Patients were asymptomatic
or presented hardly mild symptoms (in women hirsutism and/or menstrual
dysfunction). In 41 persons, 10 men and 31 women basal and ACTH-stimulated
17-hydroxyprogesterone (17-HP) concentrations were measured. A diagnosis of
21-OH-deficient NCAH was considered in patients with the basal 17-HP elevated
or with the stimulated 17-HP level more than or equal to 10 ng/ml.

Results
In 19 patients (46.3%) – 4 men and 15 women NCAH was diagnosed. Fourteen
patients had both elevated basal and stimulated 17-hydroxyprogesterone, while in
five cases only elevation of stimulated level was found.

Conclusions
i). Non-classic congenital adrenal hyperplasia is a common autosomal recessive
disease and in case of incidentally discovered bilateral adrenal hypertrophy
NCAH should be taken into consideration. ii). A basal 17-HP level is a useful
screening tool for NCAH. iii). ACTH stimulation tests are essential to make
proper diagnosis in some cases.

Keywords
incidentaloma, NCAH, 17-hydroxyprogesterone, ACTH.
DOI: 10.1530/endoabs.32.P41

15th European Congress of Endocrinology 2013
Vol 32
Endocrine Abstracts (2013) Vol 32
Effect of glucocorticoids treatment on anthropometric parameters and sexual maturation rating in salt wasting and simple virilizing forms of congenital adrenal hyperplasia in Pakistani boys

Muhtasib Akram, Madhu Shahbaz, Misbah Riaz, Shaista Aslam, Gulben Shahid,nazfar Ahmed Naseem, Fahim Tahir 
Department of Zoology, PMAS Arid Agriculture University, Rawalpindi, Pakistan; Department of Zoology, Government College University, Lahore, Pakistan; Pakistan Institute of Sciences (PIMS), Children Hospital, Islamabad, Pakistan; Department of Reproductive Physiology, National Institute of Health, Islamabad, Pakistan; Pakistan Science Foundation, Islamabad, Pakistan.

Con genital adrenal hyperplasia (CAH), caused by lack of 21-hydroxylase, impairs cortisol secretion, which increases ACTH release that results in hyperplasia of adrenal glands and increased secretion of adrenal androgens. Elevated androgen concentration leads to increased skeletal maturation, early pubertal development and diminished pubertal growth. Treatment with glucocorticoids averts early puberty but may abruptly slow down growth. The effect of exogenous glucocorticoids on adrenal and kidney functions, anthropometric parameters and sexual maturation rating was examined. Based on chronological age, twenty three (14 salt wasting (SW) and 9 simple virilizing (SV) types) male CAH patients were divided into group-I (2 patients of < 1 year), group-II (4 patients of 1-2 years), group-III (15 patients of 3-8 year) and group-IV (2 patients of 9-11 years). SW types were treated with hydrocortisone twice a day (20 mg in the morning and 10 mg at night) along with a single dose of flumone F (0.1 mg), whereas SV patients were treated with hydrocortisone twice a day (20 mg in the morning and 10 mg at night). CAH patients were compared with normal age matched controls (20 boys/group) before and following treatment. Regardless of age group and type of CAH, 17-OH P concentrations significantly decreased, concentrations of creatinine and urea were normalized but rennin activity remained unaffected in all patients. Concentrations of sodium and potassium were normalized in SW form, whereas cortisol concentrations were decreased, concentrations of creatinine and urea were normalized but rennin activity remained unaffected in all patients. Concentrations of sodium and potassium were normalized in SW form, whereas cortisol concentrations were decreased, concentrations of creatinine and urea were normalized but rennin activity remained unaffected in all patients. Concentrations of sodium and potassium were normalized in SW form, whereas cortisol concentrations were decreased, concentrations of creatinine and urea were normalized but rennin activity remained unaffected in all patients. Concentrations of sodium and potassium were normalized in SW form, whereas cortisol concentrations were decreased, concentrations of creatinine and urea were normalized but rennin activity remained unaffected in all patients.

In conclusion, appropriate glucocorticoids doses restored adrenal and kidney functions, normalized most of anthropometric parameters but did not affect sexual maturation rating.

DOI: 10.1530/endoabs.32.P42

P43

Overt and subclinical hypercortisolism in patients with diabetes mellitus and obesity

Alexander Dreval, Irina Komerdus, Anastasiya Murzina, Olga Nechaeva, Raiza Tishenina, Elena Borodina & Galina Anaskina
Moscow Regional Research Clinical Institute N.A. Vladimirsly, Moscow, Russia.

Background
It has been hypothesized that patients with type 2 diabetes mellitus (DP) are very suspicious to have hypercortisolism, especially those which a high HbA1c level. The prevalence of hypercortisolism also could be high in obese patients (OP). Methods
To 111 DP (male:female, 1:3: 58 (50: 64) years) old, HbA1c, 9.5 ± 2.2%, and 39 OP (male:female, 2:1, 72 (20: 26) years old) 1 mg dexamethasone suppression test (DST-1) have been done. If post-DST-1 cortisol level was > 50 nmol/l (positive result), the 2 mg/day for 48 h dexamethasone suppression test (DST-2) was made. If cortisol level exceeded 50 nmol/l after DST-2 (positive), subclinical hypercortisolism (SH) was suspect, and MRI, MSCT were done. Results
Positive results was found in 39% of OP after DST-1 and reduced to 10% after DST-2. Only in one case (25%) abnormality was found (pituatory adenoma). In DP DST-1 was found in 42% of cases after DST-1 and reduced to 11% after DST-2. Among OP with positive DST-2 we incidentally revealed two patients with overt hypercortisolism (confirmed thereafter). Most (75%) of the DP and OP with SH had post-DST-2 cortisol level between 50 and 140 nmol/l. At the same time two patients with overt hypercortisolism had post-DST-2 cortisol level >140 nmol/l. There were not differences between HbA1c level in DP with negative and positive DST-1 and DST-2 (P = 0.3). We made seven groups of DP depending on their HbA1c level. We did not find any differences in percent of patients with SH between groups. UFC and morning serum cortisol levels were higher in DP than in OP (P < 0.05). Because DP were significantly older than OP (P < 0.05), the two groups matched on age and BMI were created. Only the morning serum cortisol level was still higher on DP (P = 0.04).

Conclusion
Diabetic patients are highly suspicious on subclinical and also overt hypercortisolism. In some of them even overt hypercortisolism can be missed. Obese patients also had high percentage of SH, but the group was small. The cut-off level of post-DST-2 cortisol 140 nmol/l can miss a lot of patients with SH.

DOI: 10.1530/endoabs.32.P43

P44

Association of a variant of V281L of 21-hydroxylase gene CYP21A2 with simple virilizing and salt wasting types of CAH in Pakistani population

Muhtasib Shahbaz, Qaiser Mansoor, Maleeha Akram, Misbah Riaz, Azhar Beg, Shaista Aslam, Gulben Shahid, Maizhar Qayyum, Afzaal Ahmed Naseem, S.S.R. Rizvi & Muhammad Ismail
1Department of Zoology, PMAS Arid Agriculture University, Rawalpindi, Pakistan; 2Institute of Biomedical and Genetic Engineering (IBGE), Islamabad, Pakistan; 3Department of Zoology, Government College University, Rawalpindi, Pakistan; 4Pakistan Institute of Sciences (PIMS), Children Hospital, Islamabad, Pakistan; 5Pakistan Science Foundation, Islamabad, Pakistan.

Con genital adrenal hyperplasia (CAH) is an autosomal recessive disorder caused by deficiency of 21-hydroxylase (CYP21P), which inhibits adrenal synthesis of cortisol and aldosterone. The reduced cortisol synthesis leads to increased ACTH secretion, which results in adrenal gland hyperplasia, accumulation of steroid precursors and excessive adrenal androgen production, causing pseudoprecocious puberty. The study aimed at determining variance in two SNPs, I172N and V281L of CYP21A2 gene in twenty male CAH (13 salt wasting and 7 simple virilizing) patients and 20 age-matched controls. Genomic DNA was extracted and PCR-RFLP analysis was done. The genotypic frequency of wild type for two SNPs in case of controls and patients were 0.9, 1.086, and 0.63% respectively. The heterozygous frequencies were 0.1, 0.0, 0.14, and 0.16% respectively. The PCR product of CYP21A2 I172N digested by Hind III gave bands of AA genotype comprised of a segment of ~168 bp. The frequency of this genotype was 0.9% in controls and 0.86% in patients. Similarly, the genotypic frequency of other genotype AT, comprising segments of 168, 142, and 26 bp was 0.1% in controls and 0.14% in cases. The genotypes did not differ significantly between the two groups.

The prevalence of hypercortisolism also could be high in obese patients. OP.

Methods
To 111 DP (male:female, 1:3: 58 (50: 64) years) old, HbA1c, 9.5 ± 2.2%, and 39 OP (male:female, 2:1, 72 (20: 26) years old) 1 mg dexamethasone suppression test (DST-1) have been done. If post-DST-1 cortisol level was > 50 nmol/l (positive result), the 2 mg/day for 48 h dexamethasone suppression test (DST-2) was made. If cortisol level exceeded 50 nmol/l after DST-2 (positive), subclinical hypercortisolism (SH) was suspect, and MRI, MSCT were done. Results
Positive results was found in 39% of OP after DST-1 and reduced to 10% after DST-2. Only in one case (25%) abnormality was found (pituatory adenoma). In DP DST-1 was found in 42% of cases after DST-1 and reduced to 11% after DST-2. Among OP with positive DST-2 we incidentally revealed two patients with overt hypercortisolism (confirmed thereafter). Most (75%) of the DP and OP with SH had post-DST-2 cortisol level between 50 and 140 nmol/l. At the same time two patients with overt hypercortisolism had post-DST-2 cortisol level >140 nmol/l. There were not differences between HbA1c level in DP with negative and positive DST-1 and DST-2 (P = 0.3). We made seven groups of DP depending on their HbA1c level. We did not find any differences in percent of patients with SH between groups. UFC and morning serum cortisol levels were higher in DP than in OP (P < 0.05). Because DP were significantly older than OP (P < 0.05), the two groups matched on age and BMI were created. Only the morning serum cortisol level was still higher on DP (P = 0.04).

Conclusion
Diabetic patients are highly suspicious on subclinical and also overt hypercortisolism. In some of them even overt hypercortisolism can be missed. Obese patients also had high percentage of SH, but the group was small. The cut-off level of post-DST-2 cortisol 140 nmol/l can miss a lot of patients with SH.

DOI: 10.1530/endoabs.32.P43

P45

Long-term efficacy of pasireotide in a patient with Cushing’s disease and diabetes: results in the short term are not always predictive of long-term response

Laura Trentinetti, Marina Cardinaletti, Carolina Concettoni, Giorgia Marchelli, Marco Boscaro & Giorgio Arnaldi
Division of Endocrinology, Polytechnic University of Marche Region, Ancona, Italy.

The management of Cushing’s disease (CD) can be problematic, particularly when the disease persists following pituitary surgery. Here we report the case of a 55-year-old woman with CD that persisted after repeat transphenoidal surgery. The patient had an overt phenotype with facial rubor, central obesity with supraclavicular fat accumulation, cervical fat pad and proximal muscle weakness. She had received anti-hypertensive drugs and insulin for diabetes mellitus.
P46

Autonomous aldosterone secretion as a significant cause of arterial hypertension: the effectiveness of targeted therapy

Labrini Papanastasiou, Theodora Pappa, Stelios Fountoulakis, Panagiotis Tsouanas, Athina Markou, Vaios Tsiovos, Marina Anastasakou, Chrisanthi Marakaki, Dimosthenis Mallipoulos, Theodora Kounadi & George Padiatis
Department of Endocrinology and Diabetes Center, ‘G Gennimatas’ General Hospital, Athens, Greece.

Introduction
The prevalence of autonomous aldosterone secretion (AAS) in hypertensive subjects varies due to the use of various suppression tests and cut-off values. Our aim was to evaluate the prevalence of AAS in hypertensive subjects and test the anti-hypertensive effect of targeted treatment of the renin angiotensin II aldosterone system (RAAS) in AAS subjects.

Description of methods/design
We investigated 336 hypertensive subjects with and without adrenal adenoma and 83 age- and sex-matched normotensive subjects, with normal adrenal glands on computerized tomography. Serum aldosterone (ALD) and active renin levels (REN) and the aldosterone/active renin (ALD/REN) ratio were measured before and after a modified fluorocortisone suppression test (FDST - fluorocortisone suppression test after dexamethasone administration). Normal cut-offs were obtained from the controls (ALD levels post-FDST 82 pmol/l and ALD/REN post-FDST 25 pmol/mIU per l).

Results
By applying the combination of serum ALD post-FDST levels and the ALD/REN post-FDST ratio, the prevalence of AAS in hypertensive subjects was 31.3%. We found positive correlations between systolic (SBP) and diastolic (DBP) blood pressure over 4 mEq/l. Using this methodology for detection of AAS an increased prevalence of AAS was found in hypertensive subjects. Targeted treatment of AAS subjects adequately controlled their blood pressure.

Conclusions
Using this methodology for detection of AAS an increased prevalence of AAS was found in hypertensive subjects. Targeted treatment of AAS subjects adequately controlled their blood pressure.

DOI: 10.1530/endoabs.32.P46

P47

Cushing’s syndrome: source of ectopic secretion of acth found after 20 years of follow-up
Katicha Bajuk Studen & Marija Pfeifer
University Medical Center Ljubljana, Ljubljana, Slovenia.

A 59-year-old lady presented with Cushing’s syndrome in 1991. Hormone testing revealed that it was due to ectopic secretion of ACTH. However, even after a comprehensive diagnostic workup, the source of ACTH secretion was not found. Since the symptoms (arterial hypertension and diabetes) were not successfully controlled with drugs, bilateral adrenalectomy was performed and the patient was put on hydrocortisone and fludrocortisone. The patient was then followed annually in the outpatient clinic. After 15 years of follow up, the ACTH levels started to rise: at first gradually and then duplicated in the year 2011. Morphologic diagnostic procedures, which became more accurate and easily accessible in the meantime, were repeated then. CT of the thorax revealed a 4 cm big tumorous formation in the left lower lung lobe. Unfortunately, we were not able to get a representative biopsy sample with bronchoscopy. The lesion was intermediate metabolically active on PET–CT and was positive for somatostatin receptors on octreoscan. Both studies were negative for possible secondary lesions in other parts of the body. The tumour was successfully removed with video assisted thoracic surgery and histologically confirmed to be a carcinoid. The cells of the tumour stained positive for ACTH. The control serum levels of ACTH were suppressed and stayed suppressed until now. In conclusion, we report a case of ectopic ACTH secreting tumour that was found after 20 years of follow-up and then successfully removed. Two things are important for planning care in the future and focusing possible research in such patients: i) since many tumours are small at least in the early stages, more accurate diagnostic methods provide a greater chance to find them. They should be repeated periodically (at least every few years). ii) It is important to efficiently control the cortisol excess, until the tumour is found.

DOI: 10.1530/endoabs.32.P47

P48

Glucose tolerance in Cushing’s disease
Imene Rachdi, Emma Hauvat, Leila Ben Sulem, Ines Kamoun, Zinet Turki & Claude Ben Slama
National Institute of Nutrition, Tunis, Tunisia.

Cushing disease (CD) is a rare affection due to an ACTH secreting pituitary adenoma with a hypercorticism as main consequence. The aim of this study was to assess glucose tolerance anomalies in CD.

Patients
Twenty-one patients with a diagnosed CD were included; The majority of them (77.3%; n = 17) were female. Mean age was 34.2 (19–54 years) and mean BMI 31.9 kg/m² (25.9–45.7). Mean progression period of CD was 21.8 months (5–72). Catabolic signs and hypertension were present in respectively 85.7% (n = 18) and 68% (n = 15) of cases. Mean average of basal plasmatic cortisol, cortisol after low-dose dexamethasone-suppressing test and basal ACTH were respectively 851 nmol/l (287–2373), 529 nmol/l (169–1515 nmol/l), and 119 pg/ml (59–328). Pituitary lesion on MRI was a microadenoma (diameter <1 cm) in 54.4% of cases (n = 12) and a macroadenoma in the other cases.

Results
A pre-existing diabetes was present in 8 patients with a mean HBA1C at 11.4% (10.8–12%). In the other patients, fasting plasma glucose and OGTT were performed and revealed five cases of normal glucose tolerance, four of pre-diabetes, and four of diabetes.

Conclusion
Comparative study between patients having normal glucose tolerance (n = 5) and those with pre-diabetes or diabetes (n = 16) showed that patients having glucose tolerance anomalies had a higher age (36.5 vs 26.8 years, P = 0.047) and more frequent catabolic signs (16/16 vs 2/5; P = 0.008) than patients without glucose anomalies. No other correlation was found between glucose tolerance and clinical, biological or radiological features.

Glucose tolerance anomalies are common in CD. These anomalies seem to be positively correlated to the age and to the presence of catabolic signs.

DOI: 10.1530/endoabs.32.P48
P49
European Adrenal Insufficiency Registry: a comparative observational study of glucocorticoid replacement therapy
Bertil Eckman1, David Fitts2, Claudio Marelli3, Robert Murray4, Marcus Quinkler5 & Pierre Zelissen6
1University, Linköping, Sweden; 2ViroPharma Incorporated, Pennsylvania, USA; 3ViroPharma SPRL, Maastricht, Belgium; 4Leeds Teaching Hospitals NHS Trust, St James’s University Hospital, Leeds, UK; 5Charité University of Medicine, Berlin, Germany; 6University Medical Center Utrecht, Utrecht, The Netherlands.

Introduction
A once-daily modified-release formulation of hydrocortisone (Plenadren®) has been developed to better mimic physiological cortisol secretion in the treatment of patients with adrenal insufficiency (AI). Here, we describe EU-AIR, an ongoing post-authorization observational study (registry) designed to collect information on AI management and to assess the long-term safety of Plenadren® compared with traditional glucocorticoid replacement therapies in routine clinical practice.

Design
Patients with AI (primary or secondary), not participating in an interventional clinical study, are eligible for inclusion. The registry focuses on intercurrent illness, adrenal crisis, and serious adverse events. Other data collected include mortality, adverse drug reactions, dose changes, metabolic parameters, bone mineral density/content, and concomitant therapies. At enrolment, comprehensive demographic and baseline data, aetiology of AI and details of glucocorticoid replacement therapy, are collected electronically. Safety data and treatment information will be collected at subsequent clinic visits. The overall dataset will be analysed and, additionally, stratified according to patient subgroups (e.g. patients with hypertension, diabetes and/or other hormone deficiencies). All medical care decisions, including whether to treat with Plenadren® or conventional glucocorticoids, are made by the registry physician and patient.

Results
Approximately 20 centres in Germany, The Netherlands, Sweden, and the UK have been selected to participate in the study. Recruitment began in August 2012. As of 19 January 2013, the study had been initiated in eight centres and the total number of patients enrolled was 155. Primary analysis will be performed when 1800 patient-years of exposure have been achieved for each patient group (Plenadren® vs other replacement therapies). Reports will be provided to the European Medicines Agency every 6 months.

Conclusion
EU-AIR provides an opportunity to document evidence that will inform future clinical practice in the treatment of patients with AI.
DOI: 10.1530/endoabs.32.P49

P50
Oncocytic adrenal carcinoma with production of testosterone and cortisol: case report
Michal Krcma & Eva Dvorakova
Teaching Hospital Plzen, Plzen, Czech Republic.

We describe case of 29-year woman with no concomitant illnesses in her history and with negative family history in sense of adrenal or cancer disease. She came first in February 2012 for secondary hypomennorrea lasting for 3 months, hirsutism and worsening of acne. Laboratory examination reveals markedly elevated free testosterone (9.6 nmol/l) and slightly elevated morning cortisol (687.4 nmol/l) with almost no suppression in low dose dexamethasone suppression test (1 mg) and elevated DHEA-S. On CT scan was diagnosed multinodular adrenal tumor 70×45 mm (60 Hu) in right adrenal gland. Left adrenal was normal. In lower part of right liver lobe was small hypodense locus 21×15 mm suspected to metastasis. Feochromocytoma was excluded by suppression test (SIT) was used as the confirmatory test. PAC cut-off used in SIT was 10 ng/dl in this study. The confirmatory test was applied to all 134 patients with positive ARR. The confirmatory test was found to be positive in six patients (0.8%). The prevalence was determined to be 6/768 (0.8%). The prevalence was 4.6 and 1.7% upon PAC cut-off values of 5 and 7.5 ng/dl were used respectively. The median values for potassium were found to be 4.5 (3.1–6.4) and 3.5 (2.9–4.2) in essential hypertensive and PA groups respectively (P < 0.001). Three of the six patients (50%) with PA had hypokalaemia. The prevalence of PA was found to be 0.8%. More epidemiological studies are needed in the different regions of the country to evaluate the prevalence of PA in Turkey.

DOI: 10.1530/endoabs.32.P50

P51
Prevalence of primary aldosteronism among hypertensive population in Trabzon City, Turkey
Ekrem Algün, Ömer İnceçayır, İnan Anaforoğlu, Kerem Ersoy & Semih Ayhan
Department of Endocrinology and Metabolism, Trabzon Kanuni Education and Research Hospital, Trabzon, Turkey.

Introduction
There have been no studies on the prevalence of primary aldosteronism (PA) in Turkey. In this study, the prevalence of PA among the hypertensive population was investigated.

Methods/Design
The study was conducted among hypertensive patients, aged 16–88 years, who visited the out-patient clinic of Endocrinology from January 10th, 2011 to September 30th, 2011. 768 of the 774 consecutive hypertensive patients volunteered to participate. The blood pressure, height and weight were measured in all patients. The duration of the hypertensive disease, antihypertensive drug therapy, other concurrent diseases and addictions (e.g. smoking) were determined in all patients. After an 8-h fast, blood samples were collected for the determination of blood urea nitrogen, serum creatinine, sodium, potassium, plasma aldosterone concentration (PAC), and plasma-renin activity (PRA). Care was taken to ensure normal potassium serum levels in all patients before serum aldosterone/PRA ratio (ARR) test and a liberal intake of salt.

Results
ARR was found to be positive (ARR > 20) in 134 of the 768 patients. Saline infusion test (SIT) was used as the confirmatory test. PAC cut-off used in SIT was 10 ng/dl in this study. The confirmatory test was applied to all 134 patients with positive ARR. The confirmatory test was found to be positive in six patients (0.8%). The prevalence was determined to be 6/768 (0.8%). The prevalence was 4.6 and 1.7% upon PAC cut-off values of 5 and 7.5 ng/dl were used respectively. The median values for potassium were found to be 4.5 (3.1–6.4) and 3.5 (2.9–4.2) in essential hypertensive and PA groups respectively (P < 0.001). Three of the six patients (50%) with PA had hypokalaemia.

Conclusion
The prevalence of PA was found to be 0.8%. More epidemiological studies are needed in the different regions of the country to evaluate the prevalence of PA in Turkey.

DOI: 10.1530/endoabs.32.P51

P52
Adrenal metastases: aetiologies and outcome
Faiza Boutekedjiret, Mohammed Bendali & Farida Chentli
Department of Endocrine and Metabolic Diseases, Bab Oued Hospital, Algiers, Algeria.

Introduction
Adrenal metastases used to be rare in endocrinology compared to others adrenal tumours, and deemed to have a dire prognosis. Our aim is to analyze 13 cases in order to study their morphological aspects, their causes, and their outcome.

Subjects and method
Thirteen cases were studied over a long period of time (2000–2012). All of them had biological, hormonal, and radiological assessments.

Results
We had ten men and three women, mean = 58.2 (33–72). They consulted for an aching back or abdomen (n = 6), and for weight loss (n = 3). The adrenal mass was discovered incidentally by ultrasounds in 3 cases, and after an adrenal crisis in one case. On CT scan they were bilateral (n = 9) and unilateral (right adrenal) in 4 cases. Mean size = 43.5±4 mm (11–100 mm). They were generally well limited (13), heterogeneous (3) and with low density (2), but much vascularised. For adrenal function, the cortisol was normal or very low, and sometimes high (error, stress, collision tumour??). Other metastases were located in bones (n = 3), lymph nodes (n = 2), brain (1), liver (1), pulmonary (n = 1), and pituitary (n = 1). They

Endocrine Abstracts (2013) Vol 32
survived 7.75 months (1–24). The primary cancer was: pulmonary (n = 8), pleural (n = 1), thyroid (n = 2), and unknown origin (3).

Conclusion
Adrenal metastases are rare (1.08/year). They prevail in males. They are associated to other metastases, but they can be discovered incidentally. They are generally large, bilateral and much vascularized. For their cause, pulmonary cancer is in the first position, but all other cancers can be the cause. Their dire prognosis can be worsened by an adrenal crisis; for this they should be recognised very soon.

DOI: 10.1530/endoabs.32.P52

P53
Adrenal inclusion in testicular: about six cases
Ali El Mehdi Haddam1, Nora Soumeya Fedala2, Djamila Meskine3 & Farida Cheniti4
1Endocrinology Bologhine Hospital, Algiers, Algeria; 2Endocrinology Bab El Oued Hospital, Algiers, Algeria.

The adrenal enzyme deficiency leads pseudopuberty in later diagnosis or in the absence of treatment. The existence of testicular enlargement in boys can be related to adrenal inclusion. We report six observations about this pathology: Two brothers of 2 and 12 years old with 11β-hydroxylase and four patients of three, five, height and ten years old with 21-hydroxylase deficiency. The reason of consultation was the development of the penis and pubic hair with a testiculary enlargement. Hormonal balance was in favor of early pseudopuberty (FSH average, 0.15 [μl]; LH average, 0.02 [μl] and testosterone average, 8 [mg/ml]). Testicular ultrasonography objectified increased volume and testicular hypocogynes nodules. Tumor markers (HCG and ACE) were negative. Replacement and suppressive therapy by glucocorticoids is undertaken. The evolution was marred by regression of secondary sexual characteristics, reduced testicular size, increasing its echnogenicity and loss of nodules. During a reevaluation ten years later, a large heterogeneous testicular nodule is found in the fourth boy. Tumor markers were elevated. Orchidopexy is decided. The intratesticular adrenal inclusion is rare. It is the result of a cortical defect with a delay in diagnosis. Reduction of testicular volume after glucocorticoid therapy is a good predictor of disease control. However, a long term of follow up is necessary because a possibility of tumor degeneration is not exceptional.

DOI: 10.1530/endoabs.32.P53

P54
Hyperaldosteronism in patients with hyperparathyroidism: three cases
Teresa Ruiz Gracia, Francisco Fernandez Capel, Nuria Fuertes Zamorano, Emilia Gomez Hoyos, Martin Cuesta Hernandez, Alfonso Calle Pascual & Teresa Ruiz Gracia, Francisco Fernandez Capel, Nuria Fuertes Zamorano, Ismael Gavilán-Villarejo, Cristina López-Tinoco, Laura Larraín-Escandon, Pilar Rodán-Caballero, Inmaculada Gavilán-Villarejo, Cristina Lozón-Tinoco, Cristina Cossio-Sanchez & Manuel Aguilar-Diosdado

Introduction
Hyperaldosteronism can induce elevated parathyroid hormone (PTH) levels, presumably by increasing calcitriol. Furthermore, PTH stimulates aldosterone secretion in vitro, and increases angiotensin-II-stimulated aldosterone release. In a patient with hyperaldosteronism and hyperparathyroidism, PTH receptors were detected in aldosteronoma tissue. We present three patients sent to an endocrinologist for treatment/follow-up of primary hyperparathyroidism, with a delay in diagnosis. Reduction of testicular volume after glucocorticoid therapy is a good predictor of disease control. However, a long term of follow up is necessary because a possibility of tumor degeneration is not exceptional.

Case 1
A 74-year-old male presented calcium(Ca): 11.1 mg/dl, PTH (IRMA) 71 mg/l. Office BP: 160/95 mmHg, on losartan (100 mg), amiodipine (10 mg), hydrochlorothiazide (25 mg), and atenolol (50 mg). Ultra sound: parathyroid adenoma. He rejects parathyroid surgery. Treatment: cinacalcet 30 mg/day. CAP: Baldre 352/3 = 117.3, 1 h: 339/2 = 169.5, 2 h: 408/3 = 136. He rejects adrenal catheterization/surgery. Treatment: eplerenone 50 mg b.i.d.

Case 2
A 68-year-old female is referred following parathyroidectomy for hyperplasia. Pre-surgical Ca: 11.4 mg/dl, PTH/IRMA): 84 pg/ml. Office BP: 200/100 mmHg on losartan (50 mg), hydrochlorothiazide (12.5 mg), atenolol (50 mg). CAP: Baldre 174/4 = 43.5, 1 h: 224/4 = 55.5 2 h: 170/5 = 34. The patient rejects catheterization/surgery. Treatment: eplerenone 50 mg b.i.d.

Case 3
A 81-year-old female presents Ca: 10.9 mg/dl, PTH (ChL) 129 pg/ml. Office BP: 175/90 mmHg on nebivolol (5 mg), lercardipine (20 mg), and furosemide (40 mg). Parathyroid disease not detected by Ultrasound. CAP: Baldre 203/2 = 101.5, 1 h: 129/6 = 21.5, 2 h: 169/9 = 18.7. Treatment: spironolactone (100 mg/24 h), cinacalcet (30 mg/day).

Conclusions
The cases of hyperaldosteronism associated with hyperparathyroidism were detected in the clinic of a single endocrinologist over 2 years, suggesting that the association is not infrequent, and underlying the importance of ruling out hyperaldosteronism in patients with hyperparathyroidism and moderate/severe or resistant hypertension.

DOI: 10.1530/endoabs.32.P54

P55
Analysis of data of the patients with Cushings disease with use of Moscow Region’s database
Irina Komerrudis, Alexander Drevael, Anastasia Murzina, Oleg Bogatyrev, Timur Britvin, Ivan Demidov & Olga Nechaeva
Moscow Regional Research Clinical Institute n.a. Vladimisky, Moscow, Russia.

Introduction
To analyze clinical, laboratory and anamnestic data of the patients with Cushings disease (CD) we conducted a CD database.

Methods
One hundred and eighty patients with CD were investigated in MRRCI from 1975 year. To all of them in 2011 the invitation letter was sent. In only 22 patients we could confirm diagnosis of CD according to their medical documentation. Three patients died to 2011. From 2009 to 2012 in 16 patients CD were newly diagnosed. So, now in our database 38 pat. (38 males, 3 males) with laboratory and histologically confirmed CD.

Results
The age of patients at diagnosis was 39.2±12.1 y.o. Duration of their complaints – 36 (22.75) mo. BMI – 34.2 ± 6.8. 71.5% of patients were obese. One patient noted weight decreasing. In 15.7% of cases relatives of the pat. had malignancies, in 13% – endocrine diseases. In 48% of patients additional endocrine diseases revealed. In 48% of pat. glucose intolerance was newly diagnosed (17% – glucose intolerance, 83% – DM). In all patients pathology of cardiovascular system were find (hypertension – 100% (SBP – 187 ± 30, DBP – 110 ± 16), heart failure – 11%, MI – 3%). Pulmonary embolism – 5%. Gastrointestinal diseases – 83%, urinary tract diseases – 24% (urothilathias – 11%). Psychiatric disorders – 42.1%. Osteoporosis – 24%, osteopenia – 38%. Skin affection – 53% (mostly pityriasis versicolor). Infections of various organs – in 72% of patients. Laboratory changes. UFC was luthal in 66%, cortisol level after LHST – 618,3 ± 318,9 mmol/L. Mean of cortisol suppression after HEST – 803 ± 18.1%, suppression more then 50% revealed in 96% of pat. Pituitary MRI revealed macroadenoma in 14%, micro – 55%, no abnormalities – 31%. Treatment. The only neurosurgery (N) was done to 15 pat., radiotherapy only (R) – 5 pat. – N + R – in 2 pat. Adrenalectomy + Nore R – in 14 pat. One pat. refused from surgical treatment and receive medication. Efficiency. Secondary adrenal insufficiency – 61%, remission – 13%. Relapse of CD – 23%. 1 pat. (3%) died before treatment.

Conclusion
The database shows high prevalence of different complications of CD, endocrine and non endocrine diseases in relatives, effectiveness of treatment. High prevalence of relapse after treatment tend to lifelong monitoring of the patients.

DOI: 10.1530/endoabs.32.P55

P56
Evaluation of monitoring protocol for adrenal incidentalomas in our area
Isabel Mateo-Gavira, Francisco Javier Vilchez-López, Laura Larraín-Escandon, Pilar Roldán-Caballero, Inmaculada Gavilán-Villarejo, Cristina López-Tinoco, Cristina Coseria-Sánchez & Manuel Aguilar-Diosdado

Introduction
According to the latest recommendations, monitoring protocol for adrenal
Incidentalomas includes: hormonal determinations annually for 4 years and imaging at 6, 12 and 24 months. The objectives of this study are: i) to define the clinical features, natural history and clinical management of adrenal incidentaloma in our area, ii) to evaluate the performance of the current monitoring protocol.

Methods

Retrospective study including patients diagnosed with adrenal incidentaloma between 2007 and 2012 in our area. Epidemiological and clinical data were analyzed, as well as the morphological and functional characteristics at diagnosis and during follow-up.

Results

Ninety six patients were included (55.2% male, mean age 61.38 ± 12.15 years). 74.3% were overweight or obese (mean BMI of 29.66 ± 4.94 Kg/m²), 51% had hypertension, 32.3% dyslipidemia, 25% diabetes and 20.8% osteoporosis. 63.6% of the cases were detected by computed tomography, performed in most patients by digestive (21.1%) or genitourinary pathology (21%). 48.4% of adrenal incidentalomas were located in the left gland, 8.4% were bilateral and mean size at diagnosis was 26.6 ± 20.2 mm. 2 cases of Cushing’s syndrome and two of pheochromocytoma were detected at the initial evaluation and six patients underwent surgery for larger than 40 mm incidentaloma. Biopsy confirmed a case of adrenal carcinoma. At two and four years of follow up, 98.86% maintained normal function (only one phaeochromocytoma diagnosis at 6 months), and no significant changes in size were observed (mean resizing at two year evaluation was 0.56 ± 2.3 mm, P = 0.103).

Conclusions

In our area, no significant changes were detected in either the size or hormonal function in incidentalomas initially diagnosed as non-functioning; so the efficiency of systematic application of current protocol should be reassessed.

DOI: 10.1530/endoabs.32.P56

P57

Impact of antihypertensive drugs, sodium intake and potassium plasma concentrations on plasma aldosterone and plasma renin activity

Tijana Lalic1, Milos Zarkovic1,2, Jasmina Ciric1,2, Biljana Beleslin1,2, Mirjana Stojkovic1,2, Milos Stojanovic1,2, Tanja Nisic1, Slavica Savic1 & Bozo Trobojivic1,2

1Clinic for endocrinology, diabetes and metabolic disorders KCS, Belgrade, Serbia, Serbia, 2School of medicine Belgrade university, Belgrade, Serbia, Serbia.

Introduction

Primary aldosteronism (PA) is a group of disorders which are characterized by inadquate and non-suppressible production of aldosterone. The prevalence of PA is increasing in hypertensive population. The golden standard of screening for primary aldosteronism, determination of aldosterone/plasma renin activity (ARR), is influenced by numerous exogenous and endogenous factors. Testing cannot always be conducted under optimal conditions.

Objective

To determine influence of antihypertensive drugs and concentrations of potassium and sodium in blood and urine on values of aldosterone and plasma renin activity.

Methods

In this retrospective study, we analyzed medical reports of patients admitted to Department of thyroid gland disease in the period from 2008 to 2011. All of them were evaluated for anthropometric (weight, height, waist circumference, biochemical profile (including fasting glucose and oral glucose tolerance test, lipids), and clinical blood pressure. In processing data, statistical methods descriptive analysis, Student t-test and univariate linear regression were applied.

Result

Of 137 patients, there were more patients with resistant hypertension (53.28%) than with adrenal tumors (46.72%). Most patients used calcium channel blockers. Treatment with alpha blockers and calcium channel blockers does not influence ARR. Beta blockers and ACE inhibitors can influence ARR and diuretics and vasodilators have definite influence. Diabetes mellitus can have higher risk of false negative results. Urine sodium excretion is significantly correlated with plasma aldosterone and serum potassium. Plasma aldosteron and PRA are significantly correlated with concentrations of electrolytes in urine.

Conclusion

Increased prevalence of primary aldosteronism necessitates need for accurate and better diagnostics.

Keywords: primary aldosteronism drugs sodium potassium correlations.

DOI: 10.1530/endoabs.32.P57

P58

A case of Addison’s disease caused by systemic disseminated tuberculosis: mimicking lymphoma on F-18 FDG PET-CT

Junsung Moon, Byungsam Park, Jsung Yoon, Hyoungwoo Lee & Kyuchang Won

Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, Republic of Korea.

Addison’s disease is most commonly caused by autoimmune adrenalsitis. But, adrenal tuberculosis is still major cause in developing countries, that usually caused by hematogenous spread of pulmonary tuberculosis. Systemic tuberculosis causing Addison’s disease has been rarely reported. We present a case of Addison’s disease caused by disseminated tuberculosis which was mimicked as lymphoma on F-18 FDG PET-CT (PET-CT).

Sixty eight-year-old woman visited with dyspnea for 3 days. She presented with about 10 kg of weight loss, general weakness, and nausea for 3 months. There were no history of pulmonary tuberculosis and medicatations like steroids. Her skin and oral mucosa were hyperpigmented and non-tender enlarged lymph nodes were palpated in both axilla and inguinal area. The levels of serum cortisol (<1.0 μg/dl) and aldosterone (<10 pg/ml) were low and the level of serum ACTH was high (843.50 μg/ml). Cortisol response was decreased in rapid ACTH stimulation test. Then, she was prescribed prednisolone 15 mg/day and fludrocortisone 0.05 mg/day. After few days of medication, her symptoms were started to improve. On fluid analysis of left pleural effusion, there were no evidences of tuberculous pleurisy or malignant cells. Multiple lesions with increased FDG uptake were seen in PET-CT: neck, intrathoracic, intraabdominal, axillary, iliac and inguinal lymph nodes, both palatine tonsils, adenoids, and both adrenal glands. In the view of these results, the lymphoma was highly suggested. The results of Core needle biopsy of left axillary lymph node was chronic granulomatous inflammation with negative PCR for M. tuberculosis or non-tuberculobus mycobacterium. With positive result of Mantoux skin test, we clinically diagnosed as tuberculosis and started empirical antituberculous treatment. After 2 months of treatment, left pleural effusion was disappeared. After 9 months of treatment, the FDG uptaken lesions were disappeared in follow-up PET-CT. Now, she is free of symptoms with prednisolone 5 mg/day and fludrocortisone 0.05 mg/day.

DOI: 10.1530/endoabs.32.P58

P59

Cardiovascular risk in Cushing’s syndrome

Samnia Oudlakbia, Yamuna Arabi, Meriem Bensalah & Zahra Kermali

Central Hospital of the Army, Algiers, Algeria.

Introduction

Cushing’s syndrome is rare but severe because of his association with multiple complications and particularly increased cardiovascular factors. This complications determine a mortality rate four times higher than in general population.

Object

The aim of our study was to evaluate the prevalence of cardiovascular factors in Cushing’s syndrome.

Subjects and methods

Twenty-five patients with Cushing’s syndrome were retrospectively evaluated from 2008 to 2011. All of them were evaluated for anthropometric (weight, height, waist circumference, biochemical profile (including fasting glucose and oral glucose tolerance test, lipids), and clinical blood pressure.

Results

The mean age was 35.6 years, and the sex ratio 4/1 (females/males). 86% of the patients were overweight and 57.3% had high waist circumference. 76.3% of the patients had hypertension, 69.5% had impaired glucose tolerance or diabetes, 48% had hypoHDLemia and 35.2% had hypertriglyceridemia.

Conclusion

Control of all cardiovascular risk factors should be one of the primary goals during the follow-up of these patients as remission from hypercortisolism is difficult to achieve and cardiovascular risk can persit even after remission.

DOI: 10.1530/endoabs.32.P59

Endocrine Abstracts (2013) Vol 32
P61

Severe hyperglycemia due to cortisol producing adrenal carcinoma

Birgit Harbeck, Matthias Berndt, Sven Süße, Morten Schütt & Hendrik Lehnert
University of Lübeck, Lübeck, Germany.

Introduction

Adrenal carcinomas are rare aggressive endocrine tumours with an incidence of 1–1.7 per 1 000 000. Sixty percent of patients present with symptoms of excess hormone secretion, most commonly as hypercortisolism, with or without virilisation due to accompanying androgen secretion. Tumours without clinical hormonal excess most often present with symptoms such as abdominal discomfort or back pain due to tumour growth.

Case report

A 72-year-old male patient with a history of type 2 diabetes mellitus was admitted to the hospital with severe hyperglycemia. Medical history revealed arterial hypertension and a lesion of the left adrenal gland (44×36 mm). Laboratory evaluation showed elevated levels for leucocytes, glucose and HbA1c as well as low levels of potassium. Initial chest X-ray showed a suspicious left hilus. Further studies, including CT thorax and MRI of the abdomen, showed evidence of multiple pulmonary, lymphatic, muscular and mediastinal metastases. Bone scintigraphy was inconspicuous. Owing to clearly progress of adrenal tumour size, a CT/MR imaging was performed.

Blood tests showed elevated levels of cortisol, DHEA, androstenedione and 17-OH-progesterone. ACTH was suppressed. Dexamethasone suppression test showed no suppression. In conclusion metastasised adrenal carcinoma was suspected. Biochemical evaluation was followed by a sonographically controlled biopsy of the mediastinal metastasis which confirmed the diagnosis of a hormonally active adrenal carcinoma. A chemotherapy with mitotane, 5-FU and streptozotocine was started. Potassium was substituted. Hyperglycemia was controlled by an intensive insulin therapy. Hypervirilisation persisted but unfortunately the patient eventually decided against ketoconazole or any further therapy.

Conclusions

An adrenal carcinoma may present with severe hyperglycemia and hypokalaemia. Further investigations, including endocrine testing and imaging, are needed to detect the underlying tumour.

DOI: 10.1530/endoabs.32.P61

P62

Metastatic adrenocortical carcinoma presenting with concomitant secretion of glucocorticoid, mineralocorticoid, androgen, and catecholamines: a case report

Sufak Akın1, Selcuk Dagsden1, Efîl Yüksel1, Kadri Altıngöz1, İskender Sayek2, Dilek Ertöz Baydar3 & Tomris Erbas3
1Department of Endocrinology and Metabolism, Faculty of Medicine, Hacettepe University, Ankara, Turkey; 2Department of Oncology, Faculty of Medicine, Hacettepe University, Ankara, Turkey; 3Department of General Surgery, Faculty of Medicine, Hacettepe University, Ankara, Turkey; 4Department of Pathology, Faculty of Medicine, Hacettepe University, Ankara, Turkey.

Introduction

We report the first case of metastatic adrenocortical carcinoma (ACC) concomitantly secreting cortisol, aldosterone, catecholamines and androgens with the extensive distant metastasis at the time of diagnosis.

Case report

A 57-year-old woman referred for left adrenal mass (5.5×4.0 cm) two years after the diagnosis of breast cancer. The patient’s medical history revealed hypertension and diabetes mellitus. She has cushingoid and hyperandrogenemic appearance. Routine biochemical findings were normal, except for marked hypokalaemia. Laboratory testing showed hyperaldosteronism, hyperandrogenism, hypercortisolism and increased urinary catecholamines; plasma renin: 170 pg/ml (2.71–16.51), plasma aldosteron: 678 pg/ml (29.4–161.5), basal ACTH: 7.8 pg/ml (0–46), cortisol: 27.2 µg/dl (5–25), DHEAS: 947 µg/dl (35–430), testosterone: 301 ng/dl (0–74), free testosterone: 8.23 pg/ml (0.29–3.18), androstenedion: > 8.6 ng/ml (0.3–3.7), 17 OH-progesterone: > 20 ng/ml (0.8–1.3), urinary VMA: 16.6 mg/24h (3.3–6.6) and urinary adrenal: 43.8 µg/24 h (4–20). Loss of suppressibilility by both 2 and 8 mg dexamethasone and increased 24-h urinary free cortisol excretion (539 µg/24 h) suggested autonomous cortisol secretion. She underwent left adrenalectomy and hepatic wedge resection for metastatic lesion. Histopathological diagnosis was reported as an adrenocortical carcinoma. Immunohistochemical examination showed positive staining of neoplastic cells for synaptophysin and inhibin, while tumor cells did not express S-100. Hepatic tumor histology was reported an ACC metastasis. Her laboratory results reached normal levels after operation. After the diagnosis of metastatic ACC, the patient received palliative chemotherapy, including carboplatin and etoposide. She was died 2 years after diagnosis.

Conclusion

ACC is a rare malignancy with a poor prognosis and presents with variable clinical pictures. Hormonally active adrenocortical carcinomas most commonly secrete cortisol while the co-secretion of multiple steroid hormones is rare. This is the first case of metastasis ACC in a patient with concurrent Cushing’s syndrome, Com’s syndrome, hyperandrogenism and phaeochromocytoma at the time of initial presentation.

DOI: 10.1530/endoabs.32.P62

P63

Adrenal lymphoma: about two cases

Meriem Haddad, Nora Soumeya Fedala, Farida Chentli & Lina Akkache
Endocrinology Bab El Oues Hospital, Algiers, Algeria.

Lymphoma adrenal is a rare cause of adrenal tumor (0.5%). Bilateral primary lymphoma adrenal phenotype T is exceptional. We report two observations. MO 56 years old was hospitalized FOR exploration and therapeutic management of two large adrenal masses discovered on CT imaging after back pain, and weight loss. Physical examination revealed a patient asthenic, with no signs of hypersecretion. The rest of the examination was unremarkable and research call signs primary neoplasm was negative. A hormonal balance showed a low cortisol with a height ACTH level. This which required start hormone replacement therapy to hydrocortisone. The MRI objectivied large masses without signs of infiltration and locoregional lymph nodes without root. The patient was operated. However, given the highly invasive mass that extended, biopsy is performed. GA 31 years old has an adrenal mass revealed on the occasion of pain abdominals. She had a personal history of non Hodgkinpheno type B lymphoma treated during childhood. The clinical examination was without abnormalities. The MRI showed a heterogenous mass of 46 mm and multiple nodes. The patient receives chemotherapy. A reduction of tumor volume and disappearance of lymph nodes were observed. Additional surgery is performed. The histological study was in favor of NHL A predominance of diffuse large B cells is observed. The type T is exceptional. The clinical signs are not specific. Frequently, adrenal insufficiency
is observed indicating almost complete invasion of the adrenal gland. It is often asymptomatic which justifies its systematic research.

DOI: 10.1530/endoabs.32.P63

P64

Hypercortisolism endogenous and pregnancy: a report of three cases

Asma Chabour, Nora Soumeya Fedala, Farida Chentli, Asma Chabour & Imene Bala

Endocrinology Bab El Oued Hospital, Algiers, Algeria.

The occurrence of Cushing’ syndrome in pregnancy is a rare entity due to hypogonadism. Its diagnosis and treatment are very difficult because pregnancy causes hormonal and physical changes which can lead to confusion. In addition, the therapeutic options are limited because of reduced fetal risk. We report the observations of three patients who presented severe Cushing’ syndrome appeared in the first part of pregnancy. This is unknown despite a very evocative painting. Hypercorticism is complicated by diabetes mellitus, arterial hypertension and death fetal in utero. The paracinal exploration was in favor for no ACTH dependent hypercortisolism in two cases with a voluminous adrenocortical carcinoma (15 and 20 cm) and metastatic liver and bone and adrenal adenoma (6 mm) in the third patient. Adrenalectomy was realized to her while partial tumor excision was practiced in the others. Complementary therapy (anticortisolic and chemotherapy) is realized. The diagnosis of Cushing’s syndrome in a pregnant woman must be recognized early cause of morbidity and mortality maternal and fetal. If signs can be attributed to pregnancy such weight gain, hypertension or diabetes mellitus, other elements should attract attention as signs of hyperadrogenism, or signs of hypercatabolism. The adrenal adenomas and adrenocortical carcinomas are the two main cases. The reason for this predominance is unclear: less hypogonadism?, HCG?, oestrogens?, progestosterone?. If adenoma is effectively treated by surgery, pregnancy is very harmful scalability and prognosis of adrenocortical whose resection is often difficult and incomplete.

DOI: 10.1530/endoabs.32.P64

P65

Adrenal Medulla

Stud phenotypic study of paraganglioma extra surrenlien: about height cases

Nora Soumeya Fedala1, Ali El Mehdi Haddam2, Farida Chentli1, Djamila Meskine1 & Rahim Bey1

1Endocrinology Bab El Oued Hospital, Algiers, Algeria; 2Endocrinology Bologhine Hospital, Algiers, Algeria.

Paraganglioma is a tumor developed in expenses of the sympathetic or parasympathetic nervous system. It is a rare pathology (prevalency 1 for 30,000). These are situated on the basis of skull, at the level of neck, in the thorax and the belly. Some paraganglioma are functional and secrete catecholamines and others are diagnosed after surgery in the histological study of the operating piece. Through a retrospective study concerning height patients having paraganglioma extra surrenalen brought together in 20 years. We have specified theirs phenotypes.

Results

Reason of consultation: HTA (60%), abdominal pain (40%).

Mean age: 46.5 years (17–82), sex ratio: 1.6.

Clinical: HTA 12.5%, HTA, adrenergic signs (37.5%) signs tumors: 25%.

Hormonal balance: non functional: 37.5%; functional: 62.5%.

Imaging localization: Cervical: 1; Medastinal: 1; Retropertioneum: 5; Multiples: 1.

Size tumor: large (≥ 4 cm): 62.5%.

Surgery: Recurrence: 25%.

Neoplasia 1 case

Genetics 1 case

The paraganglioma is a tumor with various phenotypes. These are voluminous or smalls, uniques or multiple, secretant or no and have a risk of recurrence and degenerescence. This fact, it may be requiring a long term surveillance. Because of the family character of this pathology (1/3 cases) a genetic study is proposed at every diagnosis and the belly. Some paraganglioma are functional and secrete catecholamines and others are diagnosed after surgery in the histological study of the operating piece. Through a retrospective study concerning height patients having paraganglioma extra surrenalen brought together in 20 years. We have specified theirs phenotypes.

DOI: 10.1530/endoabs.32.P65

P66

Plasma free metanephrine and normetanephrine in chronic kidney disease patients

Dan Niculescu1, Genar Ismail1,2 & Catalina Poiana1

1Department of Endocrinology, Carol Davila University, Bucharest, Romania; 2Department of Internal Medicine and Nephrology, Carol Davila University, Bucharest, Romania.

Chronic kidney disease (CKD), with or without dialysis, often prompt biochemical tests for pheochromocytoma diagnosis due to high blood pressure, hemodynamic instability or association with certain genetic syndromes. Our objective was to assess plasma free metanephrine and normetanephrine in CKD disease patients, with or without dialysis.

Methods

Plasma free metanephrine and normetanephrine were measured by an enzyme-linked immunosorbent assay in 42 patients with CKD (23 on hemodialysis, six on peritoneal dialysis and 13 with stage 3–5 CKD but without dialysis), 30 patients with histologically proven pheochromocytoma and 43 control hypertensive patients. An adrenal mass was ruled out by an abdominal CT scan in all CKD and control hypertensive patients. As the upper limit of normal for both metanephrine and normetanephrine we used the manufacturer provided values. Values are presented as median (25, 75 percentile). Mann Whitney U test was used for group comparisons. For multiple testing Bonferroni correction was used.

Results

Both free metanephrine and normetanephrine levels were significantly higher in hemodialysis (90 (52, 162) and 303 (154, 356) pg/ml), peritoneal dialysis (69 (32, 100) and 312 (1940, 370) pg/ml) and CKD patients without dialysis (41 (22, 52) and 129 (68, 171) pg/ml) than in control hypertensive group (18 (13, 26) and 54 (100) and 312 (1940, 370) pg/ml). Dialysis patients (hemodialysis plus peritoneal dialysis) have higher plasma metanephrine and normetanephrine than CKD patients without dialysis. 48 and 65% of hemodialysis patients had plasma metanephrine and normetanephrine values of metanephrine and normetanephrine respectively over the manufacturer provided upper limit of normal.

Conclusion

Plasma free metanephrine and normetanephrine levels are frequently elevated in CKD patients, particularly in those on dialysis. Plasma free metanephrine levels rise well in the pheochromocytoma range.

DOI: 10.1530/endoabs.32.P66

P67

Succinate dehydrogenase subunit B mutations modify human neuroblastoma cell metabolism and proliferation

Benedetta Zampetti1, Elena Ranipelli1,2, Tonino Ercolino3, Rossella Fucci1,1, Roberto Felici1, Daniele Guasti1, Valentino Giachè1, Daniele Bani1, Alberto Chiarugi1 & Massimo Mannelli1,3

1University of Florence, Florence, Italy; 2University Ospedaliera Universitaria Careggi, Florence, Italy; 3Istituto Toscano Tumori, Florence, Italy.

Paragangliomas (PGLs) are rare neuroendocrine tumors. About 30–40% of these tumors are mutated in different susceptibility genes, including those
Adrenal ganglioneuroma (AGN) is a rare neoplasm derived from the neural crest. It can be found along the paravertebral sympathetic plexus. Mean age at presentation is below 20 years. Most patients with AGN are asymptomatic and diagnosis is usually incidental. Case report

Fourty-three-year-old man with a personal history of hypertrophic cardiomyopathy was referred to our Endocrinology unit, after a biopsy of a left supraclavicular node. Initial extension study was conducted in December 2010 that included: a whole body CT, which showed multiple infiltrative lymphadenopathy and MRI of abdomen, where a 3.5 cm, well defined, spherical and homogeneously hypodense right adrenal mass was found. Also, PET scan confirmed multiple infiltrative lymphadenopathy, as well as infiltrative subcutaneous implants on both sides of the neck. Hormonal study was performed to exclude hyperfunction of the adrenal mass, which included: 24-h urinary free cortisol, 1-mg overnight dexamethasone suppression test, morning plasma cortisol, ACTH, renin, aldosterone, plasmatic catecholamines and its metabolites in plasma and urine, all of them within the normal range. After excluding hyperfunction of the adrenal mass and not being able to exclude secondary infiltration of NHL, chemotherapy for treating NHL was started. After completing chemotherapy cycles no changes in size or morphology were seen in the adrenal mass, suggesting that it was independent of NHL. Consequently, a laparoscopic right adrenalectomy was performed. Pathological study showed an AGN.

Conclusions
This is the first case of AGN described in a patient with a NHL. Adrenal masses are common findings in patients with hematological diseases that may be secondary to metastatic infiltration in up to 25% of cases. However, it should take into account all possible causes of adrenal masses, including the AGN.

DOI: 10.1530/endoabs.32.P69

Bone and Osteoporosis

P70 Bone loss in inflammation-mediated osteoporosis: a role for the P2×7 receptor?
Torben Kvist, Soveiag Petersen, Anja Frederiksen, Susanne Syberg, Niklas Jorgensen & Peter Schwartz, Copenhagen University Hospital Glosstrup, Glosstrup, Denmark.

Bone loss in chronic autoimmune inflammatory diseases is a major clinical problem. Inflammation-mediated osteoporosis (IMO) is the first animal model of generalized osteoporosis resulting from inflammation. The P2×7 receptor, an ATP-gated ion-channel, is primarily expressed on immune and bone cells. ATP is now seen as a novel inflammatory mediator, with P2×7 as main target of the pro-inflammatory activity. The P2×7-receptor has a regulatory role in bone formation and – resorption. In addition, P2×7-receptor knock-out (KO) mice have shown an attenuated immune response.

Aim
To investigate the role of the P2×7 receptor in IMO.

Method
Fourteen-week-old male mice entered the IMO protocol (75 WT and 75 KO). Fifteen mice were sacrificed at baseline, 30 mice injected with silica (Talc) were sacrificed at 10 and 20 days, (15 mice at each time point). The remaining 30 mice were injected with vehicle and sacrificed at 10 and 20 days, (15 mice at each time point). The experiment was repeated with P2×7 KO mice (Pitzer). Bone mineral density (BMD) was measured by PIXImus. Spleen was collected and weighted. Blood, spine and hind legs were collected for further analysis; strength test and histomorphometry. Data: mean ± s.d.

Results
In WT animals, the spleen weight was higher in the Talc injected mice (WT: baseline 86 ± 13 mg, vehicle 109 ± 32 mg and Talc injected 131 ± 44 mg). No difference in KO.

Spine BMD was significantly lower at 20 days compared to baseline in WT vs Talc (ANCOVA weight corrected: P = 0.032). Moreover, at 20 days spine BMD was significantly lower in the Talc WT group compared to vehicle (0.046 vs 0.051 g/cm; P = 0.009). In the KO animals no significant difference was found at 20 days between vehicle and Talc group (0.052 vs 0.052 g/cm) (ns).

Conclusion
P2×7 might be involved in the inflammation-mediated osteoporosis.

DOI: 10.1530/endoabs.32.P70
Abstract withdrawn.

DOI: 10.1530/endobriefs.32.P71

P72

Circadian rhythm of circulating sclerostin in healthy young men
Santosh H Shankarnarayan1,2, & Rupa Ahluwalia1,2, Amanda Hamilton1, Dong Liu Baraclough3, William D Fraser3 & Jiten P Vora2
1Singleton Hospital, Swansea, UK; 2University of Liverpool, Liverpool, UK; 3Royal Liverpool and Broadgreen NHS Trust Hospital, Liverpool, UK; 4Norwich Medical School, Norwich, UK.

Introduction
It is recognised that osteocytes, by secreting sclerostin plays a more central role in bone homeostasis. Sclerostin is a physiological inhibitor of bone formation. By binding to the LRP5/6 receptor sclerostin inhibits the Wnt signalling pathway. A cross-sectional study was undertaken to ascertain whether an endogenous sclerostin circadian rhythm exists in healthy individuals.

Subjects and methods
Six healthy young men with normal BMD were admitted overnight. Blood samples were drawn every hour for 24 h samples obtained centrifuged immediately. The serum/plasma was separated and frozen at −70 °C for later analysis. An enzyme linked immunoassay (Biomedica, Austria) was used to measure sclerostin. All samples were assayed in duplicates. The inter and intra assay CV% being 12.3 and 5% respectively.

Statistical analysis
CHRONOLAB 3.0 (Universidade de Vigo, Vigo, Spain) a software package validated for analyzing biological time series by least squares estimation was used. Our results indicate, despite the existence of a circadian rhythm for sclerostin it does not seem to either directly influence or be influenced by PTH secretion. However the strong correlation of sclerostin to bone markers and phosphate with a zero lag indicates a direct influence of yet another factor on sclerostin circadian rhythm and bone homeostasis.

DOI: 10.1530/endobriefs.32.P72

P73

Cross-correlation of circulating sclerostin over 24 h to PTH, phosphate and bone markers in healthy young men
Santosh H Shankarnarayan1,2, Rupa Ahluwalia1,2, Amanda Hamilton1, Dong Liu Baraclough2, William D Fraser3 & Jiten P Vora1
1Royal Liverpool and Broadgreen NHS Trust Hospital, Liverpool, UK; 2University of Liverpool, Liverpool, UK; 3Norwich Medical School, Norwich, UK; 4Singleton Hospital, Swansea, UK.

Introduction
Osteotropic hormones demonstrate circadian rhythms which are integral to bone homeostasis. Sclerostin is a physiological inhibitor of bone formation. We have established that Sclerostin has a distinct circadian rhythm with a nocturnal peak. Analysis was performed to determine the relationship of the Sclerostin levels to PTH, Calcium, Phosphate, iCTX and P1NP in healthy young men.

Methods
Six healthy young men with normal BMD were admitted to our research facility. Blood samples drawn hourly for 24 h from 0400 h were centrifuged immediately. The serum/plasma separated was frozen at −70 °C. PTH, Calcium, Phosphate, iCTX and P1NP were measured. An enzyme linked immunoassay (Biomedica, Austria) was used to measure Sclerostin.

Statistical analysis
Cross-correlational analysis was performed to determine the relationships between the 24 h profiles for Sclerostin, PTH, Calcium, Phosphate, iCTX and P1NP. This determines the correlation between two time series of equal length that have been paired, data point by data point, then one of the time series is shifted by one or more time points (lag time) and the correlation process is repeated. Time series for the groups were derived by calculating the mean value at each time point for all subjects.

Results
Secretory patterns of sclerostin Vs. PTH and Calcium demonstrate no definite correlation during the 24 h period. A positive correlation was noted between sclerostin and phosphate, iCTX, P1NP with correlation co-efficients of 0.637, 0.627, 0.666 respectively. The changes in the sclerostin preceded iCTX by 1 h, but zero lags between sclerostin Vs phosphate and P1NP.

Conclusion
Our results indicate, despite the existence of a circadian rhythm for sclerostin it does not seem to either directly influence or be influenced by PTH secretion. However the strong correlation of sclerostin to bone markers and phosphate with a zero lag indicates a direct influence of yet another factor on sclerostin circadian rhythm and bone homeostasis.

DOI: 10.1530/endobriefs.32.P74

P74

Bone quality, as measured by trabecular bone score (TBS), in patients with primary hyperparathyroidism
Cristina Elies-Vainicher1, Marcello Filopanti1, Serena Palmieri1, Fabio Massimo Ulivieri2, Valentina Morelli3, Volta V, Zhukouskaya1, Elisa Cairoli1, Rosa Pino2, Antonella Naccarato2, Uberta Verga2, Alfredo Scillitani1, Paolo Beck-Peccoz2 & Iacopo Chioldini1
1Unit of Endocrinology and Diabetology, Department of Clinical Sciences and Community Health, Fondazione IRCCS Cà Granda, University of Milan, Milan, Italy; 2Unit of Nuclear Medicine, Fondazione IRCCS Cà Granda, University of Milan, Milan, Italy; 3Unit of Endocrinology, “Casa Sollievo della Sofferenza”, IRCCS, San Giovanni Rotondo, Foggia, Italy.

The fracture risk in primary hyperparathyroidism (PHPT) is partially independent of bone mineral density (BMD) and seems to depend on decreased bone quality, which is still reliably assessed only with invasive techniques. Trabecular bone score (TBS) is a grey-level texture measurement acquired during a dual X-ray absorptiometry (DXA) lumbar spine scan and it has been recently proposed as index of bone quality. This study is aimed to assess the role of TBS in predicting vertebral fractures (VFx) in PHPT patients.

We prospectively enrolled 92 PHPT patients (18 eugonadal males and 74 post-menopausal females, aged 62.7 ±10.1 years) and 98 age-, gender- and BMI matched controls. In all subjects, TBS and BMD at spine (L2) and femur (FN) were assessed (reported as Z-scores) by DXA and VFx by X-ray. Among the 92 PHPT patients, we also report the available longitudinal BMD, TBS and VFx data after 24 months of follow-up for 20 subjects operated on and for 10 conservatively treated. PHPT patients had lower BMD (LS −0.74 ±1.14, FN −0.67 ±0.84) and TBS (−3.9 ± 1.8), and higher prevalence of VFx (43.5%) than controls (0.5 ±1.46, 0.05 ± 0.85, −0.98 ± 1.07 and 8.2%, respectively, P<0.0001). The presence of VFx was associated with TBS (OR 1.6, 95% CI 1.2 – 21, P<0.001) regardless of LS BMD, age, BMI and gender. TBS showed the best compromise between sensitivity (75%) and specificity (61.5%) for detecting VFx as compared to BMD (LS 31% and 75%, FN 64% and 65%, respectively). After 24 months, in the 20 patients surgically treated, no new VFx occurred and BMD tended to increase (Z-score change LS 29.9±3.14% and FN 30.2±39.3%, P=NS), while TBS increased significantly (52.8 ±46.6%, P=0.004). In the 10 patients conservatively treated MBD and TBS tended to decrease (Z-score change LS −11.1±46.1%, FN −29.7±45.3%, TBS −139±3.5%, P=NS). In the 3 patients with a new VFx, TBS decreased significantly (Z-score change −441.6 ±217.9%) as compared to those without new VFx (−9.4 ±14.9%, P<0.05), at variance with BMD (LS −40±10% vs 1.4 ±50% and FN −36.7±103% vs −13.3±16.1, P=NS).

Conclusions
In PHPT, bone quality, as measured by TBS, is reduced and improves after surgery. TBS appears to be more useful than BMD in detecting PHPT patients at risk of fractures.

DOI: 10.1530/endobriefs.32.P74
Calcium homeostasis in women with non-metastatic breast cancer with osteoporosis after a single-dose of denosumab: a pilot study
Stylianos Mandanas, Konstantinos Touliis, Lemonia Mathiopoulou, Eftergi Margaritzidou, Konstantinos Georgopoulou, Maria Boudina, Alexandra Christioulidou & Kalliopi Pazioutou-Panagioutou
Theagenio Cancer Hospital, Thessaloniki, Greece.

Introduction
Women with non-metastatic breast cancer form a distinct subpopulation in which calcium homeostasis in response to treatment with denosumab has not been extensively investigated.

Methods
Female patients with osteoporosis, who were eligible for treatment with denosumab, were prospectively enrolled (2011-2012) and divided into two groups; Group A consisting of patients with either no history or benign diseases non affecting bone metabolism (n=24 controls) and Group B patients with non-metastatic breast cancer (n=18). Documentation of renal impairment, disorders of parathyroid function or the presence of bone metastases served as exclusion criteria. All patients were administered a single-dose of denosumab under standard calcium and vitamin D supplementation. Serum calcium, phosphorus, parathyroid hormone (iPTH) and 24 h urine calcium were measured at days 0, 7 and 180. Primary outcomes were the development of hypocalcaemia and secondary hyperparathyroidism.

Results
At baseline, groups were comparable in age, calcium and iPTH levels. No events of hypocalcaemia were recorded. Overall, incidence of secondary hyperparathyroidism was found to be 45.5% one week after administration of denosumab. Interestingly, at day 180 incidence of secondary hyperparathyroidism was higher in Group B in contrast to the pattern recorded in controls, although not reaching statistical significance. At day 7, iPTH was found to be significantly higher only in Group B compared to group-specific baseline values. At day 180, borderline increase in iPTH of Group B was noted (P=0.08), whereas iPTH returned to baseline in controls.

Discussion
A pattern of delayed development of secondary hyperparathyroidism might be present in patients with non-metastatic breast cancer. It could be extrapolated that this finding might be associated with a partial functional defect in calcium sensing receptor, which has recently been implicated in the pathogenesis of breast cancer. The findings warrant further investigation.

DOI: 10.1530/endoabs.32.P75

Long-term prospective evaluation of the effects of estroprogestagen therapy on the bone mineral density of girls with Turner syndrome carrying various PvuII AND XbaI polymorphisms of ER-α
Elzbieta Sowinska-Przepiera1,2, Elzbieta Andrzyk-Mamo1, Gruzia Jazarbek-Bielecka2, Justyna Syrenicz2, Kornel Chelstowski3 & Anhelli Syrenicz1
1Department of Endocrinology, Metabolic Diseases and Internal Diseases, Pomeranian Medical University, Szczecin, Poland; 2Department of Gynecology, University of Medical Sciences, Poznan, Poland; 3Department of Laboratory Diagnostics and Molecular Medicine, Pomeranian Medical University, Szczecin, Poland.

Introduction
Reduced bone mineral density (BMD) is present in many women with Turner syndrome (TS), while hypo-estrogenism is known to play a vital role in bone mineralization disturbances. It has been suggested that genetic factors play an important role in the regulation of BMD. The aim of this study was to analyze the association between PvuII and XbaI ER-α polymorphisms and BMD in TS patients subjected to estroprogestagen (EP) treatment.

Material and methods
Fifty-four TS patients aged 17–38 (mean age 22.7 ± 8.2), along with 82 healthy controls were the subjects for this study. Baseline values of hormonal parameters, BMD and bone density markers were measured in the subjects. Subsequently, TS patients underwent 5 years EP therapy.

Results
The results of laboratory parameters and BMD were analyzed in regards to genotype and in those with with the xx and pp genotypes of PvuII. In patients with haplotypes other than XXPP, BMD z-scores were significantly higher compared to their baseline after 2 (P=0.002), 3 (P=0.001), 4 (P=0.002) and 5 (P=0.001) years of treatment.

Conclusions
Genotypes xx and pp were shown to be prognostic markers of a good response to EP treatment, while the XXPP haplotype carriers were revealed to have the risk factors for insufficient responsiveness against EP treatment in BMD control.

DOI: 10.1530/endoabs.32.P77

Effects of Denosumab treatment on insulin resistance in postmenopausal women with osteoporosis
Konstantinos Tzioras, Maria Mizamtsidi, Aikaterini Chroniaou, Georgia Vasiliou, Sofia Tagara & Andromachi Vryonidou
Korgialenio-Benakio Hospital, Athens, Greece.

Introduction
Denosumab is a new pharmacotherapy option for postmenopausal osteoporosis. It is a human monoclonal antibody against RANKL, acting as an osteoprotegerin (OPG) analog. Recently, osteoprotegerin levels were found to be elevated in type
two diabetes while insulin resistance was shown to be positively associated with decreased serum OPG levels, in healthy obese subjects. However, no study has been conducted in order to clarify the effect of anti-RANKL factors administration on insulin resistance, especially in women with postmenopausal osteoporosis.

Methods
The study population consisted of 20 non obese, non diabetic, postmenopausal women with BMI: 22.15±2.16 and age: 64.7±7.96 years. All patients had postmenopausal osteoporosis and were followed in our outpatient clinic for at least 18 months. Serum samples were collected and analyzed for fasting glucose, insulin and c-peptide levels before the initial dose of denosumab and at 6 and 12 months during treatment. HOMA index for insulin resistance (HOMA-IR) and steady pancreatic β cell function (HOMA-β) were calculated. Patients with 25(OH)D deficiency were excluded from the study. Statistical analysis was performed by using SPSS 15.0 software. Comparisons between groups were made by using ANOVA and unpaired t-test.

Results
During the study, patients' weight and 25(OH)D levels remained unchanged (P=0.749 and P=0.456 respectively). Denosumab treatment did not cause any statistically significant change on HOMA-IR (P=0.194) or HOMA-β values (P=0.507), at all timepoints of the study.

Conclusions
These preliminary data show that in non obese and non diabetic postmenopausal osteoporotic women, treatment with denosumab does not seem to have an effect on insulin resistance or steady pancreatic β cell function.

DOI: 10.1530/endoabs.32.P78

P79
Impact of the FRAX® tool and the NOGG guidelines on the indication of bone mineral density in Spanish postmenopausal women
Georgios Kyriakos1, Alfonso Vidal Casariego1, Dalia Avila Turcios1, Ana Hernández Moreno1, Alicia Calleja Fernández1, Mª Dolores Blanco Suárez2, Rocio Villar Tabo1, Maria D. Ballesteros Pomar1 & Isidoro Can Rodríguez1
1Sección de Endocrinología y Nutrición, Complejo Asistencial Universitario de León, León, Spain; 2Servicio de Radiodiagnóstico, Complejo Asistencial Universitario de León, León, Spain.

Introduction
The National Osteoporosis Guideline Group (NOGG) recommends determine BMD in patients who present an intermediate risk of osteoporotic fracture using the FRAX® tool, follow-up for low risk, and treatment for high risk. In 2011, 3163 BMD were performed in the Complejo Asistencial Universitario de León (CAULE). Since the cost for each BMD is 58.6 € (BOCYL 31/01/2011), annual spending could rise to 1*185 352. The aim was to assess whether fracture risk calculation would result in a reduction of BMD measurements made, and therefore in the costs.

Methods
Cross-sectional study in patients referred for BMD measurement in CAULE between April and December 2012. Data of risk factors included in the FRAX® were obtained using a questionnaire completed by the technical staff. The absolute risk of presenting a major or a hip fracture was calculated using the British FRAX® formula and NOGG guidelines. We excluded patients with current or previous treatments for osteoporosis.

Results
We recruited 1163 patients, of whom 542 (46.6%) were untreated. 95% were women, with a median age of 60.2 years (Interquartile Range, IQR = 14.44), 20.1% had previous clinical fractures, 17.2% were smokers, 15.5% had parents with hip fractures, 8.3% had rheumatoid arthritis, 15.7% referred risk factors for secondary osteoporosis, 9.4% were on corticosteroids and 2.2% had a high-risk alcohol consumption. The median risk for major fracture was 8.2% (IQR = 9), and for hip fracture 1.3% (IQR = 3). Applying the FRAX® tool in combination with the NOGG guidelines 55.5% had low fracture risk, 34.5% intermediate risk and 10% high risk. Extrapolation of the data shows that 30% of all BMD annually performed in CAULE could be avoided. This would mean a cost reduction of 4.44 €/year.

Conclusion
The application of the NOGG guidelines led to a decrease in BMD indications, reducing costs and improving the efficiency in management of osteoporosis.

DOI: 10.1530/endoabs.32.P79

P80
Increased IL17A serum levels associated with low estrogen levels can play a role in postmenopausal osteoporosis
Idikó Molnár1, Ilona Bohaty2 & Eva Somogyine-Vári1
1Endocrinology and Osteoporosis Centre, Debrecen, Hungary; 2Regional Centre of Hungarian National Blood Transfusion Service, Debrecen, Hungary.

Postmenopausal osteoporosis is characterized by lower bone mass, loss of structural integrity, and sometimes becomes life-threatening. The development of postmenopausal osteoporosis is multifactorial. Estrogen plays a preventing role in the bone resorption inhibiting the secretion of proinflammatory IL1 and TNFα cytokines. IL17 proinflammatory cytokite is a new candidate in the pathogenesis of osteoporosis. IL17 levels are increased in estrogen deficiency. The relationship between serum IL17A levels and estradiol levels, as well as bone mineral density (BMD) was studied in 72 post- and 22 premenopausal women. Enzyme-linked immunosorbent assay for IL17A and chemiluminescence method for estradiol detections were used. Dual energy X-ray absorptiometry (DXA) was applied for BMD measurement in the lumbar spine (L1-L4) and femoral (total and neck) regions.

The estradiol levels were significantly higher in premenopausal women compared with postmenopausal women (239.44±226.17 vs 74.21±4.44 pg/ml, P<0.0001). Increased IL17A levels were demonstrated in postmenopause in comparison with those in premenopause (3.5±0.56 vs 2.88±0.08 ng/ml, P<0.0001). Seventy eight women out of 94 had lower estradiol levels (<80 pg/ml) and demonstrated elevated IL17A levels in comparison with 16 women who had estrogen levels in the normal range (3.43±0.56 vs 3.01±0.38 ng/ml, P<0.0001). IL17A levels were higher in osteoporotic women than in osteopenic ones (3.65±0.61 vs 3.31±0.08 ng/ml, P<0.013 in lumbar region, and 4.19±2.1 vs 3.46±0.51 ng/ml, P<0.015 in femoral region). In postmenopause, the differences in BMDs between women with low and high (>3.04 ng/ml) mean of all women +2s.o.) IL17A levels were significant in femoral region, particularly in femoral neck region (0.72±0.1 vs 0.64±0.14 g/cm², P<0.007). A strong correlation was demonstrated between IL17A levels and BMDs of all studied regions in postmenopause.

The results highlighted a relationship between IL17A and estradiol levels, as well as BMDs. Estrogen deficiency in postmenopause can accelerate the bone-wasting through increased IL17A levels, particularly in femoral neck region.

DOI: 10.1530/endoabs.32.P80

P81
Effects of the tamoxifen on calcitonin producing thyroid C cells and bone in rat model of male osteoporosis
Branko Filipović1, Jasmina Pantelić1, Milica Manojlović-Stojanović1, Svetlana Trifunović1, Nataša Nestorović1, Florina Perčinčić-Popovska1,2 & Branka Sošić Jurjević1
1Institute for Biological Research, University of Belgrade, Belgrade, Serbia; 2Faculty of Veterinary Medicine, Skopje, Macedonia.

Thyroid C cells produce bioregulatory peptide calcitonin (CT), which lowers plasma calcium (Ca) and acts as an inhibitor of bone resorption. In this study we investigated the effects of tamoxifen, as a selective estrogen receptor modulator on thyroid C cells and skeletal changes in middle-aged orchidectomized (Orx) rats as an animal model of male osteoporosis. Fifteen-month-old male Wistar rats were divided into Orx and a sham-operated (SO) groups. Two weeks after gonadectomy, one Orx group was injected subcutaneously (s.c.) with tamoxifen citrate (Orx + TAM; 0.03 mg/kg b.w.) for three weeks. The SO and second Orx group were treated s.c. with vehicle alone. A peroxidase-antiperoxidase (PAP) method was applied for localization of CT in the C cells. The volumes of C cells (Vc) and their volume densities (Vv) were determined using the multipurpose M42 test system. An Imagej public domain image processing program was used to measure bone histomorphometric parameters of the proximal tibial specimens. Blood serum samples were analyzed for CT and osteocalcin (OC), and urine samples for Ca concentration. We found a significant decrease in the Vc, Vv, and serum CT in Orx rats compared with the SO. Tamoxifen treatment significantly increased Vc and serum CT compared to the Orx. Analysis of trabecular microarchitecture of tibia showed that Orx induced cancellous bone loss and marked decreases of cancellous bone area (B.Ar), trabecular thickness (Th.Th), and trabecular number (Th.N) whereas trabecular separation (Th.Sp) was significantly increased. Serum OC and urinary Ca concentrations was considerably higher in Orx rats in comparison with SO. Administration of tamoxifen significantly enhanced B.Ar, Th.Th and Th.N and reduced Th.Sp. Serum OC and urinary Ca concentrations were significantly lower than in the Orx group. These
findings indicate that tamoxifen stimulated calcitonin-producing thyroid C cells and increased trabecular bone mass in rat model of male osteoporosis. DOI: 10.1530/endoabs.32.P81

P82

The value of PRP/PRF in the treatment of bisphosphonates-induced maxillary osteonecrosis: preliminary study

Victor-Vlad Costan1-2, Mihai Liviu Ciocâ1, Eugenia Popescu1-2 & Carmen Vulpoi1,2

1UMF ‘Gr. T. Popa’, Iasi, Romania; 2Emergency Hospital ‘St Spiridon’, Iasi, Romania.

Background

Intravenous bisphosphonates treatment brings real benefits to patients with bone metastases. Unfortunately, this treatment sometimes has a difficult to treat complication, often disabling for the patients – the osteonecrosis of the jaws. A new approach in the management of this complication is the use of platelet rich plasma (PRP).

Patients and methods

Five patients aged between 62 and 72 years old (three men and two women) were included. All patients were treated with intravenous zolendronic acid (Zomeva) for bone metastases (prostate cancer, breast cancer, hepatocarcinoma, or without a known starting point) or for multiple myeloma. When presenting, all patients had intraoral protruding mandibular and or maxillary bone sequestrums. In all patients surgical debridement was accomplished, followed by covering with platelet rich fibrin (PRF) and a mucoperiosteal flap sutured in place. Both under the flap and in the surrounding gingival fibromucosa, PRP was injected. Two patients had osteonecrosis also in other areas of the jaws, presenting oral fistulas and radiographic evidence. In these cases PRP was injected in the fibromucosa adjacent to the affected area. Both PRF and PRP were prepared and used during the surgical procedure, from the blood of the patients harvested in tubes with separator gel with anticoagulant (PRP) or with procoagulant (PRF) and centrifuged at 3500 rounds/min 7.5 min.

Results

The intraoral postoperative wounds was completely healed within 10 days as well as the mucosal fistulas. In only one case a partial wound dehiscence with bone exposure was registered and healing was achieved by secondary intention.

Conclusions

Although the number of patients in the study is small, the first results of using PRP/PRF in the treatment of bisphosphonates induced jaw osteonecrosis are encouraging, both for treating the bone sequester when present, and to avoid its formation.

DOI: 10.1530/endoabs.32.P82

P83

Bone mineral density in patients with hypersomatotropism

Alla Shepelkevich1-3, Anastasiya Stopchenskaya1,3, Irina Bilodid1,3, Alla Shepelkevich1,3, Anastasiya Stopchenskaya1,3, Irina Bilodid1,3,

1Belarusian State Medical University, Minsk, Belarus; 2Healthcare Institution ‘City Endocrinological Dispensary’ of Minsk, Minsk, Belarus; 3Republic Centre for Medical Rehabilitation and Balneotherapy, Minsk, Belarus.

Background and aim

Hypersomatotropism is known to be associated with musculoskeletal disorders, particularly, osteoporosis and increased fracture rates. However controversial data about the effects of acromegaly on bone mineral density (BMD) have been published. The aim of our research was to evaluate bone mineral density (BMD) in patients with hypersomatotropism.

Materials and methods

The study included 66 patients (20 men, 44 women) with hypersomatotropism (mean age 52 ± 11.37 years, BMI 29.64 ± 4.87 kg/m²). In 64% (42 cases) acromegaly was caused by pituitary macroadenoma, in 36% (24 cases) by pituitary microadenoma. Serum GH and IGF1 concentration were elevated in all patients (6.7 ± 4.3 ng/ml, 475.9 ± 209.1 ng/ml accordingly). Control group consisted of 31 healthy volunteers (10 men and 21 women) matched for age and anthropometric data (mean age 50.72 ± 10.23 years; BMI 29.38 ± 4.81 kg/m²). Bone mineral density (BMD) was evaluated by dual X-ray absorptiometry (DXA).

Results

We observed statistically significantly lower BMD values of the lumbar spine in patients with hypersomatotropism than in control subjects (1.19 (0.09–1.37) vs 1.32 (1.26–1.37) g/m², Z = 938.5; P < 0.009). In the group of patients with hypersomatotropism older than 50 years osteoporosis was revealed in 10.9% (five patients); osteopenia – in 23.9% (11 patients) predominantly at lumbar spine (−0.08 ± 1.53 vs 21.01 ± 0.3; P < 0.05). In the group of 20 young age participants (men under 50 and women of reproductive period) low bone mass was registered at one patient (5%).

Conclusion

The results demonstrate a high prevalence of low bone mineral density at the spine in men older 50 years and postmenopausal women with acromegaly. Further investigation might be needed to predict risk factors of osteoporosis in patients with hypersomatotropism.

DOI: 10.1530/endoabs.32.P83

P84

Effects of treatment for acromegaly on bone mineral density: is pegvisomant protective on lumbar BMD?

Giulia Brigante1-2, Daniele Santì1-2, Chiara Diazza1-2, Sara De Vincenzi1-2, Giulia Ferramini1-2, Bruno Madeo1-2, Cesare Carani1-2, Manuela Simoni1,2 & Vincenzo Rochira1,2

1Chair and Unit of Endocrinology and Metabolism, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy; 2Integrated Department of Medicine, Endocrinology and Metabolism, Geriatrics, Azienda USL of Modena, NOCSAE of Baggiovara, Modena, Italy.

Background

GH-IGF1 status is important for bone health. Acromegaly affects bone status, but less is known on the role of treatments for acromegaly on bone mineral density (BMD). Pegvisomant (Peg) is effective in treating acromegaly by reducing IGF1. As serum GH is not influenced by Peg, it is not known if residual, direct GH effects on bone (not IGF1 mediated) are preserved during treatment.

Methods

To evaluate the effects of Peg on BMD, we compared five patients treated with Peg (alone or in combination) to six patients treated with somatostatin analogues (SA) and to seven patients surgically cured, not under medical therapy. All the patients had normal serum IGF1. BMD was measured by DEXA (Hologic-QDR-2000 densitometer, Inc., Waltham, MA). A t-score of ≤ 1 and ≤ 2.5 at lumbar spine (L1-L4) and at femoral neck was used for diagnosis of osteopenia and osteoporosis, respectively.

Results

Mean age of subjects (seven males and nine females) was 60.7 ± 9.8 years. At lumbar spine, 40% of Peg-patients, 33.3% of SA-patients, and 60% of not-treated patients had osteopenia; none of the Peg-patients, and 16.7% of SA-patients, and none of not-treated patients were osteoporotic. Considering the femoral neck, 60% of Peg-patients, 33% of SA-patients, and 60% of not-treated patients had osteopenia; 20% of Peg-patients and none of the other two groups were osteoporotic.

Conclusions

The percentage of osteoporotic/osteopenic acromegalic patients seems to be lower than that reported in literature. Peg seems to protect bone at lumbar spine, but this protective effect does not seem to be exerted at femoral level where, indeed, patients treated with Peg present lower densitometric values. Patients surgically cured, not under medical therapy, have higher rate of lumbar osteopenia. No data are available on bone quality, a parameter that is usually altered in acromegaly.

DOI: 10.1530/endoabs.32.P84

P85

HLA class I, Cw*01 and Cw*15 alleles can play a preventing role in serum IL17 elevation associated with postmenopausal osteoporosis in Hungary

Ilona Bolháti1, Mónika Jurásnek-Lukovics1, Éva Somogyvér-Vári2, László Kozma1, Katalin Dankó2 & Ildikó Molnár2

1Regional Centre of Hungarian National Blood Transfusion Service, Debrecen, Hungary; 2Innouendoendocrinology and Osteoporosis Centre, Debrecen, Hungary; 3Division of Immunology, 3rd Department of Internal Medicine, University of Debrecen Medical and Health Science Center, Debrecen, Hungary.

Endocrine Abstracts (2013) Vol 32
P86

Bone health in type 1 diabetes patients with celiac disease
Sunil Kumar Kota1, Lalit Kumar Meher2, Kirtikumar D Modli2 & Sratu Jammula1
1Medwin Hospital, Hyderabad, AndhraPradesh, India; 2MKCG Medical College, Berhampur, Orissa, India; 3Roland Institute of Pharmaceutical Sciences, Berhampur, Orissa, India.

Objectives
Type one diabetes mellitus (T1DM) is associated with various autoimmune conditions including celiac disease. Both these conditions are independently and variably associated with risk of osteoporosis. The current study intended to study bone health parameters and factors affecting it in patients with T1DM with serological evidence of celiac disease (CD).

Methods
A cross sectional study including 100 type one diabetes patients following up in our hospital was screened for CD bye IgA tissue transglutaminase (TTG) levels. Twenty two patients (12%) patients tested positive. Twenty age- and sex-matched T1DM (IgA TTG negative) patients served as controls. After history and physical examination, biochemical parameters including serum levels of ionized calcium, inorganic phosphorus, alkaline phosphatase, parathyroid hormone and 25 hydroxy vitamin D were measured. Bone mineral density (BMD) were measured at total body (TB), lumbar spine (LS) and left femoral neck (FN) using dual energy X-ray absorptiometry (DXA, Lunar DRX DPO). Similarly DXA scan was done at total body (TB), lumbar spine (LS) and left femoral neck (FN) using dual X-ray absorptiometry (DXA, Lunar DRX DPO). Similarly DXA scan was done for measurement of total body bone mineral content (TBBMC), bone area (TBA) and body composition. All the parameters were expressed as mean ± s.d.

Data were analyzed using online graphpad quickcalc software and P<0.05 was considered statistically significant.

Results
TBBDM (0.77 ± 0.04 vs 0.81 ± 0.05 gm/cm2) and TBBMC (801 ± 143 vs 982 ± 196) were lower in type one diabetic subjects with IgA TTG positivity (P<0.05). Similarly the total body Z-score (−1.64 ± 0.56 vs −0.46 ± 0.67), lumbar spine Z-score (−1.42 ± 0.61 vs −0.22 ± 0.83) and femoral neck Z-score (−1.48 ± 0.52 vs −0.74 ± 0.79) and TBBMC for age Z-score (−1.3 ± 0.8 vs −1.0 ± 0.9) were lower in type one diabetic subjects with IgA TTG positivity (P<0.05). However, TBBB (1038 ± 149 vs 1134 ± 156 cm2) and TBBB for age Z-score (−0.9 ± 0.9 vs −0.8 ± 0.9) did not significantly differ between the two groups.

Discussion
Celiac autoimmune is associated with reduced bone mineralization in T1DM patients. Celiac disease should be considered as a possible secondary cause of osteopenia in type one diabetic patients found to have a reduced BMD.

Conclusion
Important impact of early identification of CD in T1DM could be to prevent this important complication.

DOI: 10.1530/endoabs.32.P86

P87

Oxidative stress in middle age males with osteoporosis: correlation of hormonal pattern and plasma total antioxidant capacity
Sebastianio Raimondo1, Francesciano Ciro Tamburrelli1, Chantal Di Segni1, Mario Marisa Persano2, Roberto Festas1, Andrea Silvestris1, Elisabetta Meucci1, Alfredo Pontecorvi1 & Antonio Mancini1
1Division of Endocrinology, Department of Internal Medicine, Catholic University of the Sacred Heart, Rome, Italy; 2Department of Spine Surgery, Catholic University of the Sacred Heart, Rome, Italy.

Male idiopathic osteoporosis is an underestimated disease, despite its clinical and social importance. The biochemical mechanisms are still poorly understood even if the interaction between genetic factors and hormone environment (especially gonadal steroids and GH) plays a undoubtful role. In previous studies we demonstrated low plasma total antioxidant capacity (TAC) in hypogonadal patients. The aim of this study was to investigate oxidative stress as risk factor for bone fracture, and its relationships with endocrine milieu.

We enrolled 31 male subjects (36–72 years), all affected by back pain/spine fracture as a consequence of trivial trauma and ten healthy controls (30–48 years). TAC was determined using a colorimetric assay, using the system H2O2–metmyoglobin as source of radicals and a chromogen (ABTS), the latency time (LAG) in the accumulation of ABTS+1, spectrosopically detectable, is proportional to antioxidants concentration. An endocrine evaluation including testosterone, estradiol, insulin, IGFI, PRL, FT4, FT3, TSH levels was also performed. Finally, bone mineral density was assessed by DXA. Bone metabolic parameters were evaluated (PTH, vitamin D, osteocalcin, and β-cross laps).

Statistical evaluation was performed using Mann-Whitney U test. The prevalence of IGFI defects (52.8 ± 15.28 ng/ml) was 5/31 (suggesting GH deficiency (GHD), confirmed by GHRI–arginine test). Hypogonadism (mean testosterone levels 2.03 ± 0.46 ng/ml) was present in 4/31. The 22 patients left did not show alterations in the hormonal parameters studied. Despite mean levels of LAG were not different between patients and controls (7.27 ± 5.5 vs 75.0 ± 6.0 s), 12 out of 31 patients had low LAG levels (between 50 and 60 s) irrespective of hormonal milieu. Moreover, when considering parameters of bone metabolism we found significantly lower vitamin D levels in hypogonadal subjects, than in patients with GHD and patients with normal hormonal parameters (10.7 ± 5.8 ng/ml vs 19.7 ± 17.7 and 22.7 ± 9.7 respectively).

These preliminary data suggest a possible involvement of oxidative stress in unexplained fractures even if further investigations are needed to establish a possible correlation with anabolic hormones involved in bone metabolism. Low vitamin D levels could exert a worsening effect on osteoporosis in hypogonadal patients.

DOI: 10.1530/endoabs.32.P87

Endocrine Abstracts (2013) Vol 32
P89
Association of the (TTTA)n repeat polymorphism of CYP19 gene with bone mineral density in Greek peri- and postmenopausal women
Anastasia Markatseli1, Leandros Lazarou2, Harilaos Kostoulas2, Prodromos Sakaloglou2, Sofia Markoulka2, Stelios Tigas1, Ioannis Georgiou2 & Agathocles Tsatsoulis1
1Department of Endocrinology, University of Ioannina, Ioannina, Greece; 2Laboratory of Human Reproductive Genetics, Department of Obstetrics and Gynaecology, University of Ioannina, Ioannina, Greece.

Introduction
Aromatase is encoded by the CYP19 gene and catalyzes the conversion of androgens to estrogens, which in turn regulate skeletal homeostasis. Polymorphisms in the CYP19 gene have been studied for their association with bone mineral density (BMD) in the general population with mixed results.

Objectives
To explore the influence of the CYP19 (TTTA)n repeat polymorphism on BMD and serum levels of osteoprotegerin (OPG), receptor activator of nuclear factor-kB 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 (TTTA)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 7–12 TTTA repeats. Women carrying the (TTTA)11 or (TTTA)12 alleles had significantly higher spinal BMD than women not carrying these alleles in both the total study population as well as in postmenopausal women aged 15–18 years. Serum levels of ionized calcium, inorganic phosphorus, alkaline phosphatase, parathyroid hormone and 25 hydroxy vitamin D were measured. Bone mineral content (BMC), Bone area (BA) and bone mineral density (BMD) were measured at total body (TB), lumbar spine (LS) and left femoral neck (FN) using dual energy X-ray absorptiometry (Lunar DRX DPO). Polymorphisms of VDR gene at the Fok1 and Bsm 1 loci were detected using SYBR Green quantitative PCR.

Results
Vitamin D deficiency (serum 25-OH D3 <30 ng/ml) was observed in 43% patients. The overall prevalence of genotype for Bsm1 in this study was 33.3% Bb, 29.2% bb and 37.5% BB. For Fok1 genotype, the prevalence was 42.4% FF, 5.7% Ff and 48.3% FF. There were no significant differences in the blood parameters when classified according to Bsm1 and Fok1 genotypes. Subjects with BB genotype have significantly higher mean TB BMC (1012.2 ± 178.8 g), TBBA (1264.1 ± 186 cm²), TBBMD (0.89 ± 0.06 g/cm²) and LS BMC (0.81 ± 0.04 g/cm²) than Bb and bb (P < 0.05). They showed tendency for association with LS BMC and LSBA (P < 0.1). Bsm 1 genotype did not show an association with FN bone indices whereas Fok1 genotype did not show an association with TB, LS or FN bone indices.

Discussion
Vitamin D is important for bone health. Vitamin D deficiency is common among children and adolescents in India, in spite of abundant sunshine. With respect to the Bsm1 genotype, the Bb and bb subgroups were more prevalent (62.5%) than BB (37.5%) and were associated with worse bone health parameters. Whereas with respect to the Fok1 polymorphism, FF genotype was most common (48.3%). But there was no difference in the bone health parameters among different subgroups.

Conclusion
The present study demonstrates VDR gene polymorphism; defined by Bsm 1 genotype has an influence on total body and lumbar spine bone mass indices in post menarcheal Indian girls.

DOI: 10.1530/endoabs.32.P89

P81
Bone health in children with GH deficiency
Sunil Kumar Kota1, Lalit Kumar Meher2, Sruti Jammula3 & Kirtikumar D Modi1
1Medwin Hospital, Hyderabad, Andhrapradesh, India; 2MKCG Medical College, Berhampur, Orissa, India; 3Roland Institute of Pharmaceutical Sciences, Berhampur, Orissa, India.

Objectives
The current study intended to assess the impact of GH deficiency (GHD) on bone health after using various size corrections.

Methods
Thirty prepubescent children with GHD (male:female = 20:10, mean age ± 9.4 ± 3.5 years) were included in the study. Data on anthropometry and total body bone mineral content (TB BMC), bone area (TBBA) and lean body mass (TBBLM) by dual energy X-ray absorptiometry were collected. Anthropometric Z-scores and bone parameter Z-scores were computed using ethnic normative reference database.

Results
Mean height for age Z-score (HAZ) was −5.1 ± 1.7. Mean TB BMC for age Z-score was −9.2 ± 6.3 and mean TBBA for age Z-score was −7.1 ± 4.3. All the study children had 'short bones' with HAZ < −2. Twenty four (80%) children had 'narrow bones' (TBBA for height Z-score < −2). Twenty one (70%) children had 'light bones' (TBBC for height Z-score < −2). Mean TB BMC for age Z-scores were significantly lower than the mean HAZ (P < 0.05), indicating lower BMC after adjusting for height. Mean TBBC for TBBLM Z-score was −3.3 ± 4.2, indicating bone mineral deficit even after adjusting for TBBLM. There was no significant gender difference in any of the parameters.

Discussion
GHD in children causes low bone mineral density (BMD). Height and muscle force drive bone mineralization. International society of clinical densitometry has made it obligatory to applying size corrections. Analysis of different bone health parameters lead to the demontration that Indian children with GHD have 'short bones' (100% cases), 'narrow bones' (80% cases) and 'light bones' (70% cases).

Conclusion
Indian prepubesential GHD children had low bone mass even after applying size corrections implying need for corrective measures for their bone health.

DOI: 10.1530/endoabs.32.P91

P90
Vitamin D receptor polymorphisms and bone mass indices in post menarcheal Indian adolescent girls
Sunil Kumar Kota1, Lalit Kumar Meher2, Sruti Jammula3 & Kirtikumar D Modi1
1Medwin Hospital, Hyderabad, Andhrapradesh, India; 2MKCG Medical College, Berhampur, Orissa, India; 3Roland Institute of Pharmaceutical Sciences, Berhampur, Orissa, India.

Objective
The aim of the present study was to assess the association between vitamin D receptor (VDR) gene polymorphism and bone mass indices in Indian adolescent girls.

Methods
The current study was a cross sectional one including 100 post menarcheal girls aged 15–18 years. Serum levels of ionized calcium, inorganic phosphorus,
**P92**

**The effect of monthly Ibandronate on bone mineral density and bone turnover markers in patients with hemophilia A or B and increased risk for fracture**

Panagiotis Anagnostis1,2, Tomoleon-Achilleas Vyzantiadis2, Maria Charizopoulou1, Fotini Adamidou1, Spyridon Karra1, Aristidis Slavakis1, Vasilia Garipidou1 & Sofia Vakalopoulou1

1Department of Endocrinology, Hippokration Hospital of Thessaloniki, Thessaloniki, Greece; 2Haemophilia Center of Northern Greece, 2nd Propedeutic Department of Internal Medicine, Aristotle University, Hippokration Hospital of Thessaloniki, Thessaloniki, Greece.

**Introduction**

Haemophilia A and B has been associated with increased prevalence of low bone mineral density (BMD). However, no study has so far evaluated the effects of anti-osteoporotic therapy on BMD.

**Methods/design**

The primary endpoint of this prospective study was to estimate the effect of 12-month therapy of oral ibandronate 150 mg/month in BMD in patients with haemophilia A and B. Secondary endpoint was its effect on bone turnover markers (BTM), including serum C-terminal telopeptide of type one collagen (sCTX) and tartrate-resistant acid phosphatase band 5b (as markers of bone resorption), osteocalcin and bone-specific alkaline phosphatase (as markers of bone formation). We present an interim analysis of the first 12 months of the study.

**Results**

Ten males (aged 43.7±13.8 years, seven with haemophilia A) were included. Ibandronate resulted in a significant increase in lumbar BMD (from 0.885±0.162 to 0.926±0.177 g/cm², (z=4.9%, P=0.01)). No significant change in BMD of total hip (from 0.717±0.128 to 0.729±0.153 g/cm², P=0.963) or neck (0.741±0.135 to 0.761±0.146 g/cm², P=0.952) was noticed.

**Conclusions**

In the first study conducted so far evaluating the effect of bisphosphonates in patients with haemophilia and increased fracture risk, ibandronate significantly improved BMD in lumbar spine and reduced bone resorption. Its effect on hip BMD and bone formation markers was not significant.

DOI: 10.1530/endoabs.32.P92

---

**P93**

**Age overlooked as a risk factors for osteoporosis**

Stig Andersen, Ole Nielsen & Peter Laurberg

Aalborg University Hospital, Aalborg, Denmark.

Osteoporosis is a debilitating condition that can be prevented by timely detection and treatment. Detection requires referral for dual energy X-ray absorptiometry (DXA) that depends on risk factors. We estimated the importance of risk factors for a T-score of < −2.5 measured by spine and hip DXA in all men and women referred from general practice for a DXA scan at Aalborg University Hospital during a 3-year period. Risk factors were assessed by questionnaire and referral papers. A total of 335 women and 818 men were referred: 3042 aged 50–69 years/1726 aged 70 years or above/484 aged 80 years or above. A low T-score was found in 33.2%/21.4%/6.9% respectively (P<0.001). No risk factors were identified in 13.3%/15.3%/17.4% (P=0.10) when aged was excluded as a risk factor. Risk factor occurrence differed between the age groups 50–69/70–79/80+ years for family history (46/25%/15%; P<0.001), predisposing disease (21/50%/25%; P<0.001), steroid use (5.6/12.3%/13.2%; P<0.001), low sun exposure (12.8%/16.5%/24%; P<0.001), smoking 25/19/10%; P<0.001), and high alcohol intake (5.8/5%/2.0%; P=0.004), while not for premature menopause (21/20/15%; P=0.12), low intake of dairy products (4.3%/4.2%/5%; P=0.18), or low BMI (2.4%/2.0%/2.0%; P=0.69). Fragility fractures increased with age (women, 21/39/49%, P<0.001; men, 24/32/29%, P=0.088). In conclusion, the T-score and fracture dependence on family history, sun exposure, smoking, and alcohol intake was as expected. However, the limited change in risk factor occurrence with age suggests that age per se had too low impact on referral for DXA scanning, even though age is a major determinant of fracture risk.

DOI: 10.1530/endoabs.32.P93

---

**P94**

**Trabecular bone score and bone mineral density in Ukrainian normal women depending on duration of postmenopausal period**

Vladyslav Povoroznyuk & Nataliia Dzeryovych

Institute of Gerontology NAMS Ukraine, Kyiv, Ukraine.

**Materials and methods**

We’ve examined 122 normal women aged 40–79 years (mean age = 56.2±0.8 years; mean height = 162.6±0.5 cm; mean weight = 71.5±1.3 kg), who were divided into the groups depending on duration of PMP: without menopause (with normal menstrual cycle) (n=25), 1–3 years (n=26), 4–6 years (n=12), 7–9 years (n=18), 10–12 years (n=8), 13–15 years (n=4), 16–18 years (n=5), more 19 years (n=7). BMD of total body, lumbar spine and femoral neck and TBS (TBS Insight software package, Med-Insaps) were measured by DXA using a densitometer Prodigy, GE.

**Results**

We determined the significant decrease of TBS (L1-L4) in women with age (F=4.52; P=0.0001). Duration of PMP has a significant influence on the variability of BMD of spine (F=3.20; P=0.004), BMD of femoral neck (F=5.41, P<0.000; and TBS with normal menstrual cycle – 1.36±0.02/mm, 1–3 years – 1.31±0.02/mm, 4–6 years – 1.22±0.04/mm, 7–9 years – 1.23±0.03/mm, 10–12 years – 1.21±0.04/mm, 13–15 years – 1.16±0.06/mm, 16–18 years – 1.15±0.06/mm, more 19 years – 1.15±0.03/mm; F=5.70; P<0.000). The analysis using Scheffe’s test shows that TBS was significantly lower in women with duration of PMP more 4 years (4–6 years (P=0.003), 7–9 years (P=0.002), 10–12 years (P=0.002), 13–15 years (P=0.0003), 16–18 years (P=0.0003), and more 19 years (P=0.0002)) in compare with women without menopause; BMD of spine significantly decreased in women with duration of PMP 7–9 years (P=0.02), 10–13 years (P=0.003), and more 19 years (P=0.0001).

**Conclusion**

TBS is independent parameter which has potential diagnostic value without bone mineral density. TBS was significantly decreased with age. Duration of PMP has a significant influence on the variability of TBS, BMD of spine and femoral neck. TBS significantly decreased in women in early postmenopausal period.

DOI: 10.1530/endoabs.32.P94

---

**P95**

**Bone metabolism with special emphasis to osteoprotegerin and vitamin D3 concentrations in premenopausal women with thyroid dysfunctions**

Dominika Tuchendler1, Renata Tuchendler1, Katarzyna Skorkowska-Telcikowska1, & Marek Bolanowski2

1Department of Endocrinology, Military Hospital, Wroclaw, Poland; 2Department of Endocrinology, Diabetology and Isotope Therapy, Medical University, Wroclaw, Poland.

**Objectives**

The objective was to evaluate effects of hyperthyroidism and hypothyroidism on bone metabolism in premenopausal women with special emphasis to osteoprotegerin (OPG) and vitamin D3 (vD).

**Materials and methods**

A total of 119 women aged 18–52 years were studied (38 with recently diagnosed hyperthyroidism; 40 with newly diagnosed hypothyroidism; 41 healthy women as controls). Patients were followed up for a period of 1 year. BMD, bone turnover markers and hormonal analyses with regard to seasonal changes in 25(OH)D3 were carried out at 0, 6 and 12 months.

**Results**

On the initial evaluation lower femoral neck BMD was found in patients with hyperthyroidism compared to hypothyroidism. Higher bone markers, osteocalcin (OC) and bone collagen type one crosslinked CTX (CTX) were noted in OPG nor vD among the studied groups. After 6-month in patients treated due to hyperthyroidism than in controls and hypothyroidism. A difference was not found in OPG nor vD among the studied groups.
hyperthyroidism, higher OC was demonstrated (vs hyperthyroidism and controls) and CTX (vs controls). In this group a decrease in CTX was also demonstrated. No difference was shown in OPG among the studied groups. However, a statistically significant lower vitamin D$_3$ was demonstrated in he treated group with hyperthyroidism and the control group. In the group with hyperthyroidism decrease of OC and CTX were observed. After 1 year increase in OPG was seen in the group treated due to hyperthyroidism and hypothyroidism.

Conclusions
A negative effect on bone metabolism is observed only in the group of female patients with hyperthyroidism. Osteoprotegerin seems not to be a useful marker of bone metabolism in thyroid dysfunction. Vitamin D$_3$ was significantly decreased, independent of the season, in all groups studied.

DOI: 10.1530/endoabs.32.P95

P96
Efficacy and safety of monthly oral minodronate for the treatment of glucocorticoid-induced osteoporosis in rheumatoid arthritis patients
Fuminori Hirano, Yasutaka Takeda, Hiroki Saito, Kakuya Matsumoto & Hideo Nishimura
Asahikawa Medical Center, Asahikawa, Japan.

Rheumatoid arthritis (RA) is a chronic inflammatory disease that results in generalized bone loss and increased fracture risk. Although glucocorticoids are frequently prescribed for the symptomatic management of inflammatory disorders such as RA, extended glucocorticoid exposure is the leading cause of osteoporosis and leaves patients at a high risk of fracture. The aim of this study is to evaluate the efficacy and safety of monthly oral minodronate for the treatment of osteoporosis induced by glucocorticoid and RA itself, and to compare minodronate with weekly or daily risedronate in glucocorticoid-induced osteoporotic RA patients. Minodronate was monthly administrated to 36 osteoporotic RA patients at a dose of 50 mg for 24 weeks. Ten RA patients were treated with no bisphosphonate (group I) before minodronate treatment. In contrast, 16 or 10 RA patients were treated with weekly or daily risedronate (groups II or III), respectively, and changed to monthly minodronate. Lumber and total hip bone mineral density were measured at 0 and 24 weeks. Serum tartrate-resistant acid phosphatase 5b (TRAP-5b) and bone-specific alkaline phosphatase (BAP), parathyroid hormone (PTH), and urinary type-I collagen cross-linked-N-telopeptide (uNTx) were measured. RA activity and a mean dose (7.3±1.1 mg/day) of oral prednisolone were not significantly changed in three groups. The percentage change from baseline (0 week) in lumber and total hip bone mineral density was increased in group I and III at 24 weeks. In contrast, bone mineral density in group II at 24 weeks was not changed compared with baseline (0 week). In addition, TRAP-5b and uNTx at 24 weeks were significantly decreased in group I and III (P<0.01) and BAP was weakly decreased in all groups at 24 weeks. Moreover, serum concentration of PTH was increased in group I, but was reduced in group II and III. In addition to those data, serum calcium was decreased in group II and III, but not group I. In conclusion, monthly administration of minodronate was effective in glucocorticoid-induced osteoporosis in RA patients. Furthermore, monthly minodronate was thought to be strong bisphosphonate, as compared with daily risedronate. Especially, the effect of minodronate on the induction of secondary hyperparathyroidism might be weak as compared to that of risedronate.

DOI: 10.1530/endoabs.32.P96

P97
Change in bone mass in patients with established hyperthyroidism
Florian Toti$^1$, Dorina Ruci$^1$, Teuta Backa$^1$ & Elizama Petrela$^1$
$^1$University Hospital Center 'Mother Theresa' Department of Endocrinology and metabolic diseases, Tirana, Albania; $^2$University Hospital Center 'Mother Theresa' Department of Reumatology, Tirana, Albania.

Objectives
To evaluate the presence and the degree of osteoporosis and osteopenia in a group of patients with established hyperthyroidism from at least 6 months.

Material and methods
This study was based on a quantitative measurement of bone mineral density with no heel ultrasound densitometer (Type Pegasus). Each selected patient was recorded for the weight, height, BMI, age, and gender. No patient was previously treated for osteoporosis or osteopenia. A control group with similar data was selected from the general population, with no personal or familiar history of hyperthyroidism. None of them had a known history for osteoporosis or had received any medication for this condition. The criteria for osteoporosis were those recommended from the WHO. Osteoporosis was defined as T-score ≤ -2.5.

Results
We studied 64 patients with confirmed hyperthyroidism from at least 6 months and 38 persons of the same age and gender in healthy conditions. There were 22 males and 42 females (33/67%). Mean age 59.9±12.1 years, weight 74±2 kg, BMI 27.8 kg/m². For the control group: 38 patients (14/24 M/F), age 60.5±11.1 years, weight 69.9±12.3 kg, BMI 26.2 kg/m². The mean values of T-score for the hyperthyroid patients were −3.7±1.4 and −2.0 for the control group. 55% of patients with hyperthyroidism had severe osteoporosis, compared with only 9.5% of control group (P<0.001). The gender itself was no significant.

Conclusions
The silent osteoporosis and osteopenia is relatively frequent in hyperthyroidism, significantly more than in normal population. The stimulation of osteoclasts more than osteoblasts and alteration of remodeling cycle from thyroid hormones is believed to be the causative factor.

DOI: 10.1530/endoabs.32.P97

P98
The follow-up in patients evaluated based on quantitative ultrasound: a prospective study
Mara Carsote$^{1,2}$, Valentin Radu$^1$, Mihaela Popescu$^2$, Roxana Dusceac$^2$ and Cristina Ene$^2$, Gabriela Voicu$^1$, Mihaij Coculescu$^{1,2}$ & Catalina Poiana$^{1,2}$
$^1$Davila UMPh, Bucharest, Romania; $^2$Parhon Institute, Bucharest, Romania.

Introduction
The heel quantitative ultrasound (QUS) is a useful tool in the assessment of fracture risk especially if costs issues are involved. It might be helpful in follow-up the patients who will not be treated with anti-osteoporotic drugs.

Aim
To present the bone evaluation (DXA) after a period of time in patients who are initially assessed by both DXA and QUS.

Material and patients
This is a prospective pilot study in a group of postmenopausal women. They were not treated with anti-resorptive drugs at first evaluation, meaning central DXA (at least two sites) and heel QUS (GE Achilles). After at least one year they were re-evaluated only by DXA (because of data lack in QUS use in patients treated with anti-osteoporotics as the patients initially diagnosed with osteoporosis started therapy).

Results
Out of 360 patients who were first evaluated, 61 patients were followed-up for mean 23.53 months. The initial mean age was 55.77 years. We formed two subgroups of patients based in QUS stiffness index (SI). Lower SI than 79 U (mean 23.53 months. The initial mean age was 55.77 years. We formed two subgroups of patients based in QUS stiffness index (SI). Lower SI than 79 U

Material and methods
This is a prospective pilot study in a group of postmenopausal women. They were not treated with anti-resorptive drugs at first evaluation, meaning central DXA (at least two sites) and heel QUS (GE Achilles). After at least one year they were re-evaluated only by DXA (because of data lack in QUS use in patients treated with anti-osteoporotics as the patients initially diagnosed with osteoporosis started therapy).

Conclusions
In patients with high fragility fracture risk based on QUS, the ~2 years follow-up period of time pointed a higher number of patients with significantly BMD decreases than the group with low fracture risk. This is an argument that the DXA and QUS are two complementary methods in fracture risk evaluation.

DOI: 10.1530/endoabs.32.P98
P99
Prospective study of bone mineral density in girls treated with estrogenprogestogens for functional hypothalamic amenorrhea during late puberty in relation to the polymorphism of VDR (BsmI), ER (PvuII; XhoI), and COL1A1 genes
Elzbieta Sowinska-Przekopa1,2, Elzbieta Andrysik-Mamos3, Grazyna Jarzabek-Bielecka4, Justyna Syrenicz2, Kornel Chlechowski1 & Anhelli Syrenicz1
1Department of Endocrinology, Metabolic Diseases and Internal Diseases, Pomeranian Medical University, Szczecin, Poland; 2Department of Gynecology, University of Medical Sciences, Poznan, Poland; 3Department of Laboratory Diagnostics and Molecular Medicine, Pomeranian Medical University, Szczecin, Poland.

Introduction
The aim of this study was to verify if genetic factors influence the short- and long-term therapeutic responses to estrogenprogestagen (OP) therapy, implemented in girls with functional hypothalamic amenorrhea (FHA) in order to improve their bone mineral density (BMD).

Material and methods
The study included 84 FHA girls who underwent a 4-year sequential OP therapy with 17-β oestradiol and didrogesterone. Changes in the lumbar spine BMD were determined at the end of the therapy and 6 years after its discontinuation, and analysed in regards to PvuII and XhoI polymorphisms of oestrogen receptor-alpha gene, BsmI polymorphism of vitamin D receptor gene, and Sp1 polymorphism of the type-1 collagen gene.

Results
After 4 years of OP therapy, a significant increase in BMD was documented in the studied group. Follow-up densitometry performed 6 years after completing the therapy revealed a significant decrease in BMD level; nonetheless, the values of this parameter were still significantly higher compared to pretreatment level. Neither the particular polymorphisms nor their combinations influenced the relative change in BMD at the end of the therapy and after a 6-year follow-up.

Conclusions
Variability of genes involved in oestrogen, vitamin D and collagen metabolism does not influence the short- and long-term results of OP therapy in girls with FHA.

DOI: 10.1530/endoabs.32.P99

P100
Vertebral fracture prevalence in postmenopausal women in relation to bone mineral density (BMD)
Jovanka Novakovic-Paro, Blanka Kovacev-Zavisic, Milena Mihovic, Dragana Tomic-Naglic, Milica Medic-Stojanoska, Ivana Bajkin, Tijana Icin, Djordje Popovic & Edita Stokic
Clinic for Endocrinology, Diabetes and Metabolic Disorders, Clinical Centre of Vojvodina, Novi Sad, Vojvodina, Serbia.

Introduction
Epidemiological studies show that one half of vertebral fractures, which play an important role in estimation of future fracture risk, remain unrecognized.

Aim
To establish vertebral fracture frequency in relation to bone mineral density in postmenopausal women.

Methods
Study comprised 146 postmenopausal women. On the grounds of spine and hip DXA T-score based on WHO criteria subjects were divided to healthy, osteoporosis or osteopenia. Vertebral fractures were verified by lateral DXA scan vertebral morphometry of thoracic and lumbar spine.

Results
Vertebral fractures were found in 111 (76%) women; 58 (52.2%) in osteoporosis, 33 (29.7%) in osteopenia and 20 (18.1%) in healthy subjects. Statistically significant difference was found between age of women with osteoporosis compared to group with osteopenia and healthy group (67.86 ± 9.24 vs 62.97 ± 8.74 years; 67.86 ± 9.24 vs 61.55 ± 10.53 years; P<0.05). Statistically significant difference between patients in relation to body mass index was not found. Thoracic vertebra fractures dominated in all three groups with similar frequency of compressive and second degree wedge fractures. Statistically significant higher frequency of vertebral fractures was found in group with osteoporosis compared to healthy osteoporosis group (P<0.001). Statistically significant higher frequency of lumbar vertebrae fractures was seen in osteoporosis compared to osteopenia and healthy subjects. Higher frequency of vertebral fractures in women with osteopenia compared to healthy group was not statistically significant.

Conclusion
Lateral DXA scan can be used in estimation of fracture risk in addition to BMD, clinical and biochemical risk factors to provide better insight in individual fracture risk and help decide upon activities and therapy in fracture prevention.

DOI: 10.1530/endoabs.32.P100

P101
Vertebral fractures in women with postmenopausal osteoporosis with or without prior fragile fracture
Jovanka Novakovic-Paro, Blanka Kovacev-Zavisic, Milena Mihovic, Dragana Tomic-Naglic, Ivana Bajkin, Tijana Icin, Radoslav Pejin, Dragan Tesci, Damir Benic & Milica Medic-Stojanoska
Clinic for Endocrinology, Diabetes and Metabolic Disorders, Clinical Centre of Vojvodina, Novi Sad, Vojvodina, Serbia.

Introduction
Vertebral fragile fracture is risk factor for future vertebral and hip fractures.

Aim
To establish prevalence of vertebral fractures using lateral DXA scan of thoracic and lumbar spine in women with postmenopausal osteoporosis.

Method
Study comprised 73 women with postmenopausal osteoporosis diagnosed using spine and hip DXA. Vertebral fractures were verified by lateral DXA scan vertebral morphometry of thoracic and lumbar spine.

Results
37 (50.7%) women had prior non-vertebral fragile fracture (group A) and 36 (49.3%) did not (group B). Group A had fractures as follows: 26 (70.3%) distal radius, 2 (5.4%) hip, 3 (8.1%) ribs, 2 (5.4%) proximal humerus, 4 (10.8%) distal fibula. There was not statistically significant difference in age and BMI between two groups (67.24 ± 7.81 vs 67.58 ± 10.28 years; BMI: 26.42 ± 3.94 vs 24.76 ± 3.94 kg/m²). Average T-scores in group A were: L1-L4 = −2.5 s.d., femur neck = −1.83 s.d., hip = −1.94%. In group B: L1-L4 = −3.2 s.d., femur neck = −2.3 s.d. and hip = −2.77 s.d. There was statistically significant difference of L1-L4 T-score among groups (group A = −2.5; group B = −3.2; P<0.005). In group A 7 (18.9%) women did not have vertebral fracture, 9 (24.3%) one, 21 (56.7%) two or more and 7 (18.9%) five. In group B 8 (22.2%) had no vertebral fractures, 8 (22.2%) one, 20 (55.5%) two or more, and 11 (30.5%) had two vertebral fractures. In both groups thoracic vertebrae fractures of second degree were more frequent, with similar frequency of compressive and wedge fractures. Women in group A had statistically significant higher frequency of vertebral fractures (P<0.05) and lumbar vertebrae fractures (P<0.05).

Conclusion
Women with prior fragile fracture have greater frequency and more vertebral fractures, with lumbar vertebrae fractures with repercussions on BMD. Lateral DXA scan helps in spine and hip DXA BMD interpretation and individual fracture risk estimation.

DOI: 10.1530/endoabs.32.P101

P102
Effect of long-term valproate therapy on bone health parameters
V P Jyotsna, Rajiv Singla, M B Singh, S V Sumita & Vandita Gupta
All India Institute of Medical Sciences, New Delhi, India.

Introduction
Anti-epileptic drugs (AED) adversely affecting bone health. However, individual variations between different AEDs exist and not all AEDs are equally toxic to the bone. There is almost equipose about the effect of valproate on bone.

Methods
We conducted a cross-sectional study assessing bone mineral density with dual energy X-ray absorptiometry at the hip and lumbar spine in 33 outpatients receiving valproate for ≥1 year and 36 healthy adults. Plasma total calcium, phosphorus, intact parathyroid hormone, total alkaline phosphatase and 25 hydroxy vitamin D were determined in both groups. All participants were evaluated for daily dietary calcium intake by dietary recall method.

Results
Patients had taken 1020±575.06 g (cumulative dose) of valproate over 6.46±3.83 years of epilepsy. The mean (± S.D.) bone density in patients, as compared to...
controls, treated with antiepileptic drugs was 0.987±0.121 vs 0.940±0.094 g/cm² at the spine and femoral neck 0.858±0.146 vs 0.818±0.136 g/cm². Difference between two groups was not significant statistically. Osteopenia was present in 90.62% of controls and 85.71% of patients. Osteoporosis was present in 6.25% of patients and 14.29% of controls. Serum intact parathyroid hormone was significantly higher in patients (60.32±29.16 vs 45.16±20.00 pg/ml, P = 0.01), but the total calcium, 25-hydroxy vitamin D, alkaline phosphatase and dietary intake of calcium did not differ significantly between patients and controls. But, both groups displayed grossly low serum vitamin D (patients: 12.44±9.91 ng/dl, controls: 13.87±8.57 ng/dl) and dietary calcium intake below recommended daily allowance.

Conclusion
Our results suggest that chronic therapy with valproate does not result in significant decrease in bone density. Widespread vitamin D deficiency is still prevalent in our country.

DOI: 10.1530/endoabs.32.P102

P103
Efficacy and safety of the anabolic therapies in severe osteoporosis: experience of a team of endocrinologists and spine surgeons
Matilda Mormando1, Alessandra Fusco1, Enrico Pola1,2, Serena Piacentini1, Luigi Aurelio Nasto1,2, Debora Colangelo1,2, Sabrina Chilio1, Antonio Bianchi1, Alfredo Pontecorvi1 & Laura De Marinis1
1Division of Endocrinology, Catholic University, Rome, Italy; 2Division of Spinal Surgery, Department of Orthopaedics and Traumatology, Catholic University, Rome, Italy.

Anabolic therapies represent a major advance in the management of severe osteoporosis. Parathyroid hormone (PTH) and human recombinant PTH peptide 1–34 (Teriparatide) demonstrated an increase in bone mineral density and a significant reduction in vertebral fractures in patients with osteoporosis when given for 18–24 months. The intermittent administration of PTH or teriparatide stimulates osteoblastic function, improves bone architecture and has an additional analgesic effect.

We retrospectively analyzed the safety, efficacy and adherence to therapy with anabolic agents given for 18 months in 79 patients (FM: 72/7) with severe osteoporosis resistant to antiresorptive therapy. Patients were followed by a team of spine surgeons and endocrinologists from 2007 to 2012. Before anabolic therapy 40 patients underwent percutaneous kyphoplasty, 23 were treated with brace and 16 patients refused any orthopaedic treatment. Anabolic agents were administered as a daily injection, and vitamin D supplementation was given, when necessary. The change in BMD value was measured at the beginning of therapy and after 18 months through lumbar and femoral DEXA scan. A total of 64 patients completed the 18 months treatment with anabolic agents. 15 patients (19%) discontinued the treatment: 11 patients because of side effects occurring during the first 3 months of therapy (hypercalcemia occurred in eight patients) and for patients due to non adherence to therapy. All patients had vertebral fractures (VF) (mean number of VF 3.2±1.4) and suffered from back pain. During anabolic therapy, 31% of patients showed an improvement of back pain. At the end of the treatment, there was a substantial increase in BMD at both lumbar spine (+8.5%) and femoral neck (+5%). This study confirms that anabolic agents are safe and effective. Adherence to therapy is very high, despite the daily administration. Of note, this therapy reduce back pain in a significant percentage of patients.

DOI: 10.1530/endoabs.32.P103

P104
Vitamin D receptor, BsmI, FokI, Apal, TaqI and estrogen receptor alpha, PvuII and XbaI, gene polymorphisms in women with osteoporosis
Susana Vladoiu1, Sabina Oros1, Dana Manda1, Roxana Rosca1,2 & Olga Iana1
1C.I. Parhon National Institute of Endocrinology, Bucharest, Romania 2Carol Davila University of Medicine and Farmacy, Bucharest, Romania.

Objective
The aim of this study was to determine the frequencies of vitamin D receptor (VDR) BsmI, FokI, Apal, TaqI and estrogen receptor α (ESR1) PvuII and XbaI polymorphisms in Romanian patients and to investigate their involvement in postmenopausal osteoporosis.

Methods
The study was carried out on 82 postmenopausal women, aged over 60, divided into two groups: group 1-postmenopausal women with osteoporosis (34 subjects), group 2-postmenopausal women without osteoporosis (48 controls). The hematological and biochemical profiles were evaluated. ESR1 (BsmI and FokI) and VDR (BsmI, Apal, TaqI and FokI) polymorphisms were determined by PCR-RFLP method on genomic DNA.

Results
BsmI, FokI, Apal I and Taq I allele distribution were in Hardy Weinberg equilibrium with no significant differences between group 1 and 2. There were significant differences between distributions of PvuII, IVS-1 − 397 TC and XbaI, IVS-1 − 351 AG genotypes in osteoporosis group compared to healthy women. G allele of XbaI polymorphism seems to be a risk allele for osteoporosis (P = 0.03, OR = 7.6). No association was found between BMD and VDR polymorphisms.

Conclusions
The genotype and allele frequency distributions were in Hardy–Weinberg equilibrium excepting ESR1, Xba I, G allele that seems to be a risk allele for osteoporosis. VDR polymorphisms showed no significant difference between osteoporosis and control group.

DOI: 10.1530/endoabs.32.P104

P105
Possible benefits of PTH 1–84 therapy in pregnancy and lactation osteoporosis (PLO)
Renato Pastore
UOC Endocrinology, Ospedale Fatebenefratelli, Isola Tiberina, Rome, Italy.

Introduction
Pregnancy and lactation associated osteoporosis (PLO) is a rare condition in which women typically present with fractures, often vertebral, in the third trimester of pregnancy or in the early postpartum period. Bone loss of 3–10% at the spine and hip are seen over 3–6 months of lactation. Bone loss is related to duration of lactation and amenorrhea and is not prevented by calcium supplementation.

Methods
We studied a woman of 45 years, in the third trimester of pregnancy, who suffered from constant low back pain, which prevented her to walk properly. Three months after childbirth, she underwent by DXA severe osteoporosis characterized by multiple vertebral fractures. Bone markers as alkaline phosphatase, osteocalcin, serum β-cross laps, PTH, 25OHD, 24 h urine calcium were assessed. Secondary causes of osteoporosis were also studied by specific laboratory tests: TSH, ematology, renal and epatic function, proteins, CA125, and CA15-3. All of them were considered within normal range. Patient suffered from reflux and esophagitis. Osteogenesis imperfecta were also excluded. We choose to treat her with osteocalcinic PTH 1-84 therapy.

Results
DXA showed increase in BMD at lumbar site after 18 months of PTH 1–84 treatment. Biochemical parameters increased at the 6th and the 12th month and then reduced, as described in the literature, at the 18th month of therapy. During this period the patient showed marked improvement in the lumbar algodistrofia, being able to walk slowly.

Conclusion
As this disorder is likely to be heterogeneous in its etiology and prognosis, a thorough evaluation for secondary causes of osteoporosis should be undertaken in all cases of PLO. Results obtained in our clinical experience confirm the efficacy of PTH 1–84 therapy on high risk of fracture in PLO, documented increase of T-score at the spine, besides the increase of β-Ctx and osteocalcin levels.

DOI: 10.1530/endoabs.32.P105
P106

Influence of some traditional risk factors for osteoporosis on bone metabolism during substitution therapy of primary hyperthyroidism
Radoslav Pejin, Milena Mitrovic, Jovanka Novakovic-Paro, Dragana Tomic-Nuglic, Branka Kovacevic-Zavisic, Dragan Tesic, Milica Medic-Stojanovska, Dusan Tomic, Ivana Bajkin & Ljiljana Todorovic-Djilas
Clinic for Endocrinology, Diabetes, and Metabolic Disorders, Clinical Centre of Vojvodina, Hajduk Veljkova 1, Novi Sad, Serbia.

Relation between thyroid hormones and bone metabolism markers in hyperthyroidism is well known. Earlier studies indicate possibility of bone metabolism acceleration during the excessive replacement therapy with l-thyroxine in hypothyroid patients especially in one with other risk factors for bone metabolism impairment. This study evaluated the effect of physiological l-thyroxine treatment on bone metabolism in patients with primary hyperthyroidism.

In a study group of 30 hypothyroid patients individual l-thyroxine replacement was performed targeting euthyroid status. Bone and calcium metabolism parameters (osteocalcin-OC, alkaline phosphates-ALP, C-terminal cross-linking telopeptide of type I-Ca, Ca, ionized Ca, P), thyroid hormone levels (T3, T4, TSH) were measured before treatment and when euthyroid status was achieved.

In this study the following parameters were examined: influence of BMI, physical activity, time of menarche, duration of lactation period, number of children and occurrence of menopause before therapy and when the euthyroid status was achieved on bone metabolism markers.

Significant difference by dispersive analysis was found in bone metabolism markers concerning influence of menopause, physical activity and BMI in treated hypothyroid patients. We did not found significant difference in bone metabolism markers among groups concerning parameters like duration of lactation period or number of live born children.

Key Words
Hypothyroidism, bone and bone metabolism, l-thyroxine substitution therapy, risk factors for osteoporosis.

DOI: 10.1530/endoabs.32.P106

P107

Resolution of anaemia after curative parathyroidectomy in a patient with primary hyperparathyroidism
Panagiotis Anagnostis1, Fotini Adamidou1, Alexandra Agapidou2, Sofia Vakalopoulou2, Vasilia Garipoudo2 & Marina Kita1
1Department of Endocrinology, Hippokration Hospital of Thessaloniki, Thessaloniki, Greece; 2Department of Internal Medicine, Haemophilia Center of Northern Greece, Hippokration Hospital, Aristotle University, Thessaloniki, Greece.

Introduction
Despite the coexistence of secondary hyperparathyroidism with anaemia, hematomatological manifestations of primary hyperparathyroidism (PHPT) are rare.

Case report
A 67-year-old Caucasian female was admitted to the Department of Internal Medicine due to normocytic anaemia and hypercalcemia, diagnosed on occasion of muscle weakness and fatigability for 3 months.

Her medication included: alendronate 70 mg/week, alfacalcidol 1 μg/day, valsartan 160 mg, hydrochlorothiazide 12.5 mg/day, oxcarbazepine 900 mg/day and simvastatin 40 mg/day. Her family history was negative for diseases affecting bone metabolism. No remarkable signs were revealed from clinical examination. Initial laboratory assessment showed: hematocrit (Ht): 28.6%, hemoglobin (Hb): 9.3 g/dl, white cell count: 6760/l, platelets: 281 000/l, urea: 13 mg/dl, creatinine: 1.35 mg/dl, estimated glomerular filtration rate (eGFR): 44 ml/min per 1.73 m², serum total calcium (Ca): 14.3 mg/dl (normal: 8.8–10.6), serum phosphorus (P): 4.9 mg/dl (normal: 2.5–4.5), parathyroid hormone (PTH): 350 pg/ml (normal: 10–53), 25-hydroxyvitamin D: 7.9 ng/ml (normal: > 30 ng/ml), 24 h urinary Ca: 300 mg/24 h (normal: 0–250). Neck ultrasound showed a hypoechoic lesion 21×5.4 mm suggestive of adenoma of the right lower parathyroid gland, confirmed by Tc99m-sestamibi scan.

Regarding anaemia, comprehensive laboratory, endoscopic and imaging investigation was negative. Bone marrow biopsy and myelogramm showed normal cellularity without fibrosis.

The patient was initially managed with fluid resuscitation, i.v. farosomide and cinacalcet, after alfacalcidol and hydrochlorothiazide discontinuation, which resulted in gradual restoration of renal function and improvement of Ca (10.9 mg/dl). The patient underwent a successful parathyroidectomy, with postoperative PTH: 31.8 pg/ml, Ca: 9.8 mg/dl and P: 3.4 mg/dl.

Surprisingly, Ht and Hb returned to normal postoperatively. In particular, 3 months later, Ht was 34.5% and Hb: 11.5 g/dl, while after 12 months, Ht: 39.8% and Hb: 13.4 g/dl.

Conclusions
Successful parathyroidectomy resulted in resolution of anaemia. The etiology of anaemia is not fully elucidated. Proposed mechanisms are the development of marrow fibrosis and the inhibitory effect of PTH on erythropoiesis.

DOI: 10.1530/endoabs.32.P107

P108

A case of 23 years old woman with primary hyperparathyroidism presenting with pathological fracture and brown tumors detected by scintigraphy
M Musam Canat1, Feyza Yener Ozturk1, Selvinaz Erol1, Mehmet Uludag2 & Yuksel Altuntas1
1Sisli Efai Training and Research Hospital, Endocrinology and Metabolism Clinic, Istanbul, Turkey; 2Sisli Efai Training and Research Hospital, General Surgery Clinic, Istanbul, Turkey.

Introduction
Primary hyperparathyroidism (PHPT) occurs a peak incidence between ages 50 and 80 and the classical bone disease of PHPT or pathological fractures due to PHPT is rarely seen today. Furthermore brown tumor detected with Tc-99m MIBI scintigraphy exists in literature infrequently.

Case
A 23 years old woman presented with left arm pain admitted in Department of Orthopaedics for pathological fracture in left humerus. As a result of investigations hypercalcemia and cystic lesions in diaphysis of left humerus and many other bone localization found, then referred to our section.

Initial laboratory profile, serum calcium: 15.2 mg/dl (8.6–10.2), serum phosphorus: 2.5 mg/dl (2.6–4.5), total alkaline phosphatase: 722 U/l (35–105), 24-h urine calcium: 572 mg/day (100–321), PTH (IRMA): 3308 ng/ml (15–65), 25(OH) vitamin D: 8.98 ng/ml (25–80). Rest blood results revealed normal. Also there was no abnormality at plasma calcitonin, methanephrine, normetanephrine, anterior pituitary hormones and basal cortisol levels.

Neck ultrasound showed an encapsulated, homogeneous, hypoechoic solid mass lesion at inferior pole of right lobe of thyroid gland, largest measures 2×2×1.5 cm in dimension, contains central and peripheral vascularity. Tc-99m MIBI scintigraphy was performed and a foci of radiotracer accumulation was seen caudal to the right lobe of thyroid gland, also found accumulations on distal third of the left clavicle and the localizations of both sternoclavicular joints consistent with brown tumor.

Evaluation of bone mineral density; the lowest Z-score value in localization lumbar region and total value of the femur were recorded as (–3.2) and (–1.9), respectively. After seum calcium values lowered the patient was operated and localized parathyroid gland was excised. The pathological evaluation revealed parathyroid adenoma.

Conclusion
PHPT also occurs at a young age therefore familial hyperparathyroidism syndromes such as MEN should be investigated in these cases. Nowadays despite most patients with PHPT do not have the classic radiologic bone disease, the skeleton lesions can be seen and even lead to pathological fractures. Furthermore cystic lesions in bones can be evaluated inaccurate primary bone tumor.

DOI: 10.1530/endoabs.32.P108
A patient osteogenesis imperfecta with osteoporosis
Gulcin Cengiz Ececin, Elib Kilic Kan, Cigdem Tura Bahadir, Aysegul Attmaca, Hulusi Attmaca & Ramis Colak
Endocrinology Department, Faculty of Medicine, Onokokaz Mayis University, Samsun, Turkey.

Introduction
Osteogenesis imperfecta (OI) is a congenital, generalized connective tissue disorder characterized by severe osteoporosis and bone fragility. OI is most commonly caused by mutations in genes encoding the α-1 and α-2 chains of type I collagen or proteins involved in posttranslational modification of type I collagen. Although, no controlled studies are done, bisphosphonates are used for the treatment of OI. I.v. bisphosphonates are reported to be more effective for pain control than oral bisphosphonates. Here, we report the results of a patient with OI and osteoporosis who received cyclic i.v. pamidronate.

Case report
A 31 years old man with OI and osteoporosis admitted with generalized bone pain. He had been using alendronate 70 mg/week p.o. for 2 years with no improvement in bone mineral density (BMD) and pain. I.v. cyclical pamidronate was started at a dose of 60 mg/day for 3 days every 4 months. BMD was assessed at baseline, at 6 and 12 months of treatment. Short form-36 (SF-36) questionnaire was used to evaluate his quality of life at baseline and at 12 months. His vertebral BMD T-score was −4.2 and femur neck T-score was −2.0 at baseline. At 6th month, his vertebral BMD T-score was −3.6 and femur neck T-score was −1.6. At 12th month, his vertebral BMD T-score was −3.6 and femur neck T-score was −1.4. A significant improvement was observed in his SF-36 scores at 12th month. No adverse effects were observed due to treatment.

Conclusion
OI is a rare disease and no treatment protocol has been shown to be superior to others. I.v. bisphosphonates may be better for pain control than oral bisphosphonates. This case shows the improvement of BMD and quality of life after 1 year treatment with i.v. pamidronate, which not achieved with oral alendronate.

DOI: 10.1530/endoabs.32.P109

Fear of illness and quality of life in Greek postmenopausal women with osteoporosis
Gesthymi Mintziari1, Vasileios Golia1, Areti Triantafyllou2, Stella Leda Papageorgiou1, Evangelia Tsiga1 & Dimitrios Goulis1
1Unit of Reproductive Endocrinology, First Department of Obstetrics and Gynecology, Aristotle University of Thessaloniki Medical School, Papageorgiou General Hospital, Thessaloniki, Greece; 22nd Propedeutic Medical School, Hippokration General Hospital, Thessaloniki, Greece.

Introduction
Fear of illness and quality of life have been proven to be affected in women with osteoporosis. Fear of illness and quality of life in women with severe osteoporosis have been reported to be negatively correlated with fear of illness. This present study aims to assess the fear of illness and quality of life in women with postmenopausal osteoporosis.

Methods
Sixty postmenopausal women, aged 50–85 years were studied. Bone mineral density (BMD) was estimated in all the women with the use of Achilles InSight – Bone Ultrasonometer. Every woman who had T-score <-2.5 completed a questionnaire for assessing health related quality of life in osteoporosis (ECOS-16). Higher scores in ECOS-16 indicate lower quality of life.

Results
Twenty-five women with a mean age 70±7 years had a T-score <-2.5. Older women had greater fear of their illness (P=0.03) with age being the only variable correlated with fear of illness (P=0.05). Women with lower T-scores had reduced quality of life (P<0.05).

Conclusion
The grade of osteoporosis can significantly influence the quality of life whereas fear of illness is also influenced in older postmenopausal women. Local health services should focus on prevention and treatment of osteoporosis as well as on the support and improvement of quality of life of women living with osteoporosis.

DOI: 10.1530/endoabs.32.P110

Calcium and Vitamin D metabolism

The relationship between low maternal serum 25-hydroxyvitamin D level and gestational diabetes mellitus according to the severity of 25-hydroxyvitamin D deficiency
Sayid Shafii Zuhur, Runyaeya Selvinaz Erol, Idris Kuzu & Yuksel Altuntas
Süli Efla Training and Research Hospital, Endocrinology and Metabolism Clinic, Istanbul, Turkey.

Introduction
The results of publications investigating the relationship between low maternal serum 25-hydroxyvitamin D (25(OH)D) level and gestational diabetes mellitus (GDM) are controversial and none of these publications have investigated this relationship according to the severity of 25(OH)D deficiency. Therefore, this study was conducted to assess the relationship between low maternal serum 25(OH)D and GDM according to the severity of 25(OH)D deficiency.

Methods
We analysed 25(OH)D levels in 234 women with GDM and 168 controls. To define deficiency status, maternal serum levels of 25(OH)D were further classified into four groups (<12.5 nmol/l as severely deficient, 12.5–24.9 nmol/l as deficient, 25–49.9 nmol/l as insufficient and ≥50 nmol/l as sufficient, respectively).

Results
Women with GDM had significantly lower 25(OH)D levels compared to controls (30.8 vs 35.3 vs 36.0±16.2 nmol/l, P=0.002). However, when subgroups of 25(OH)D were analysed, GDM was significantly more common only in women with severely deficient 25(OH)D level. After adjusting for covariates including maternal age, previous history of GDM, history of type 2 DM in first degree relatives and pre-pregnancy BMI, only severely deficient 25(OH)D levels were independently associated with an increased relative risk of GDM (OR=3.95, 95% CI, 1.68–9.25, P=0.002). The odds ratios of GDM in women with insufficient and deficient 25(OH)D levels were not statistically significant (OR=1.46, 95% CI, 1.27–1.74, P=0.23, OR=1.64, 95% CI, 1.26–2.13, P=0.18, respectively).PTH concentrations were also significantly higher in women with GDM compared to controls (44.3 ±23.6 vs 38.7 ±27.6 pg/ml, P=0.016).

Conclusions
Results from this study provide novel data indicating that only severely deficient maternal serum 25(OH)D level is significantly associated with an elevated relative risk of GDM, even after adjusting for established risk factors of GDM. Large-scale, well-designed and multi-center studies are required to further evaluate this relationship.

DOI: 10.1530/endoabs.32.P111

Effects of vitamin D fortified bread on muscle strength
Veronica Mocanu, Anca Roxana Costan & Carmen Vulpoi
UMF ‘Gr. T. Popa’, Iasi, Romania.

Background
Vitamin D deficiency is common in elderly nursing home residents. It has been associated with low bone mineral density, muscle weakness, increased body sway and falls. Evidence indicates that supplementation of vitamin D in these individuals helps to improve locomotor function and general health.

Patients and methods
We evaluated, in a 12 months interval, the effects of vitamin D supplementation on grip strength in 45 nursing home residents (28 women and 17 men, aged 58–89 years) who consumed daily one bun fortified with 125 µg vitamin D3 (25(OH)D) and 320 mg elemental calcium, in order to achieve optimal blood levels of 25(OH)D >75 nmol/l. Grip strength was measured at baseline and 12 months after vitamin D supplementation, using a specific dynamometer (Baseline Squeeze Bulb Dynamometer, USA). For each hand, the highest of three attempts was noted as maximal grip strength. The average of maximum values for the left and right hands was considered as the measure of the participant’s muscle strength.

Results
Muscle strength positive correlated with locomotion functions score (P=0.034) and levels of vitamin D (P=0.046), but significant improvement of grip strength could not be proven although optimal levels of vitamin D were maintained for long term. Although optimal levels of 25(OH)D were associated with an amelioration of locomotor function, grip strength improvement was not statistically significant (P=0.570).

DOI: 10.1530/endoabs.32.P112
Conclusions
Vitamin D deficiency is only one of the conditions that affect muscle function in elderly people. Our results showed a good correlation between muscle strength and 25(OH)D levels, but sustained normalization of vitamin D levels is not sufficient for significant improvement of muscle function. Further control randomized studies may be necessary for a better understanding of the effects of long term vitamin D supplementation on the health outcomes in the elderly.
DOI: 10.1530/endoabs.32.P112

P113
Evaluation of two routinely used 25OHD assays and serum variables in patients on dialyses
Zoltan Loecei1, Laszlo Kovacs1, Dora Balogh1, Adrienn Szijarto1, Bernadette Kalman2, Gabor I. Kovacs3,5 & Erzsebet Toldy3,5
1 Department of Medicine of Markusovszky Teaching Hospital of County Vas, Szombathely, Hungary; 2 Department of Practical Diagnostics, Faculty of Health Science, University of Pecs, Szombathely, Hungary; 3Institute of Laboratory Medicine, Pecs, Hungary; 4Central Laboratory of Markusovszky Teaching Hospital of County Vas, Szombathely, Hungary; 5Institute of Diagnostics, University of Pecs, Pecs, Hungary.

The total 25-hydroxy-vitamin-D (25OHD) level can be assessed by various methods and reflects vitamin D intake. Results are influenced by the serum variables affected by dialyses.
Aims
To examine t25OHD and bioavailable vitamin D (b25OHD) by two methods in patients on peritoneal-(PD) and hemodialysis (HD).
Methods
Aims
We studied 37 HD (64 ± 15 years) and 36 PD (63 ± 18 years) patients. The t25OHD was assessed by chemiluminescence immunoassay (LIA) and electrochemiluminescence protein binding assay (PBA). Levels of PTH-biointact (PTHb) by immunometric assay, vitamin D binding protein (DBP) by turbidimetry and albumin by colorimetry were measured. The b25OHD values were calculated.

Results
The total 25-hydroxy-vitamin-D (25OHD) level can be assessed by various methods and reflects vitamin D intake. Results are influenced by the serum variables affected by dialyses.
Aims
To examine t25OHD and bioavailable vitamin D (b25OHD) by two methods in patients on peritoneal-(PD) and hemodialysis (HD).
Methods
Aims
The t25OHD levels only 12% of patients in PD, but 36% of women in the C1 group had suboptimal (<75 nmol/l) vitamin D supply. Bio25-OHD values reflecting suboptimal (<6.4 nmol/l) vitamin supply occurred most frequently (51%) in the OC and least frequently in the C1 group (15%). Levels of t25OHD were highest (P < 0.001) in the OC (100 (88 117) nmol/l) and the lowest (P < 0.001) in PRG group (41 (28 57) nmol/l). However, bio25OHD levels were lower in the OC (6.3 (5.6 8.1) nmol/l) than in the C1 group (8.1 (6.6 9.7) nmol/l) (P = 0.06). Associations were observed between t25OHD and PTH-1–84 levels in all groups (C1: r = -0.29 P < 0.05; C2: r = -0.62 P < 0.01; OC: r = -0.36 P < 0.05) except the PRG group. There was no association between t25OHD and CaAlb levels, while a correlation was detected between bio25OHD vitamin and CaAlb levels (r = 0.53 P < 0.05) in the C2 group only.

Conclusions
The total 25-hydroxy-vitamin-D (25OHD) level reflects the supply of vitamin D, but is also influenced by the levels of 25OHD binding proteins (DBP). We aimed studying t25OHD and bioavailable 25OHD (bio-25OHD) levels in healthy females with different reproductive ages.

Methods
While the DBP levels were measured by routine methods (Modular, Roche). Bio-25OHD and albumin – corrected Ca (AlbCa) were calculated in 126 healthy young women (age: 35.3 ± 15.9 years) of whom 41 took oral contraceptives (OC); 45 were without pills (C1) and 40 were pregnant (PRG). An older control group of 21 postmenopausal women was also included (C2: age: 68.5 ± 14.5 years).

Results
The highest levels of DBG were found in the PRG and OC groups. Based on the t25OHD levels only 12% of patients in PD, but 36% of women in the C1 group had suboptimal (<75 nmol/l) vitamin D supply. Bio25-OHD values reflecting suboptimal (<6.4 nmol/l) vitamin supply occurred most frequently (51%) in the OC and least frequently in the C1 group (15%). Levels of t25OHD were highest (P < 0.001) in the OC (100 (88 117) nmol/l) and the lowest (P < 0.001) in PRG group (41 (28 57) nmol/l). However, bio25OHD levels were lower in the OC (6.3 (5.6 8.1) nmol/l) than in the C1 group (8.1 (6.6 9.7) nmol/l) (P = 0.06). Associations were observed between t25OHD and PTH-1–84 levels in all groups (C1: r = -0.29 P < 0.05; C2: r = -0.62 P < 0.01; OC: r = -0.36 P < 0.05) except the PRG group. There was no association between t25OHD and CaAlb levels, while a correlation was detected between bio25OHD vitamin and CaAlb levels (r = 0.53 P < 0.05) in the C2 group only.

Conclusions
t25OHD and DBP levels may dysproportionally change. The estimates of vitamin D supply are influenced by the 25OHD fraction assessed especially in case of estrogen excess.
DOI: 10.1530/endoabs.32.P114

P115
Cinacalcet in patients with primary hyperparathyroidism (PHPT): comparison between sporadic and MEN1 PHPT
Michela Del Prete1, Vincenzo Marotta2, Valeria Ramundo3, Francesca Marielli4, Anna Chiara Carratu5, Chiara De Luca di Roseto6, Raffaella Esposito1, Antonella Di Sarno7, Annamaria Colao8 & Antonio Giugliani9
1Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy; 2Interventional Unit, Azienda dei Colli Hospital, Naples, Italy; 3Endocrinology, National Cancer Institute, Fondazione G. Pascale, Naples, Italy.

Introduction
PHPT is a common endocrine disease characterized by hypercalcemia and different degree of osteoporosis and nephrolithiasis. PHPT arises in the context of an inherited disease in 5% of cases. Multiple endocrine neoplasia type 1 (MEN1) is the commonest cause of inherited PHPT. The main therapeutic approach for PHPT is surgery, however many patients refuse or have contraindications for surgery while others, in particular those with MEN1 PHPT, have persistent/relap-
sing disease after surgery. Cinacalcet is a calcimimetic agent which has been demonstrated to be effective in the control of PHPT.
Aims
The aim of this study was to evaluate and compare the effectiveness of cinacalcet in patients with sporadic and MEN1 PHPT.

Patients and methods
Fifty patients have been enrolled: 25 of them had sporadic PHPT (7 M, 18 F, mean age 67 years) and 25 MEN1 PHPT (9 M, 16 F, mean age 41 years). Serum concentrations of PTH, calcium and phosphorus were evaluated before and 6 and 12 months after starting cinacalcet.

DOI: 10.1530/endoabs.32.P111

P114
Vitamin D supply in healthy women with different reproductive stages: is there any relationship with DBP levels?
Erzsebet Toldy1,2, Zoltan Loecei1, Dora Ezsoru Horvath1, Csaba Koppany1, Claudia Kovacs1, Emanuela Tancsics1, Bernadette Kalman3 & Karoly Raczi2
1Central Laboratory of Markusovszky Teaching Hospital of County Vas, Szombathely, Hungary; 2Department of Practical Diagnostics, Faculty of Health Science, University of Pecs, Pecs, Hungary; 31st Department of Medicine of Markusovszky Teaching Hospital of County Vas, Szombathely, Hungary; 4Department of Gynecology of Markusovszky Teaching Hospital of County Vas, Szombathely, Hungary; 5Department of Molecular Medicine of Markusovszky Teaching Hospital of County Vas, Szombathely, Hungary; 6Institute of Internal Medicine of Semmelweis University, Budapest, Hungary.

Purpose
The purpose of the study was to assess the relationship between vitamin D supply in healthy women with different reproductive ages.
Methods
15th European Congress of Endocrinology 2013

Methods

Methods
Results
Serum calcium and PTH concentrations decreased significantly in both groups (P < 0.01). There were no significant differences between sporadic and MEN1 PHPT in the rate of calcium and PTH concentration decrease after 6 and 12 months of therapy. At 12 month follow-up, the dose of cinacalcet required to normalize calcium in sporadic PHPT was 30 mg a day in 15 patients and 60 mg in 10 other patients, while in MEN1 PHPT the dose of cinacalcet was 30 mg in 8 patients, 60 mg in 11, 90 mg in 6 other patients.

Conclusions
Cinacalcet is equally effective in normalizing hypercalcemia in sporadic and MEN1 PHPT. However, MEN1-related PHPT required a higher dose of cinacalcet than sporadic PHPT to normalize serum calcium. This contrasts with preliminary published reports and might be explained by the fact that in MEN1 PHPT all parathyroid tissue is affected and hyperfunctioning.

DOI: 10.1530/endoabs.32.P115

Efficacy of vitamin D on COPD exacerbation: a double blind randomized placebo-controlled clinical trial

Mojmír Sanjari1, Akbar Soltani2, Abdolrahim Habibi Khorasani3, Mostafa Shokouhi4 & Maryam Zarinejad5
1Physiology Research Center, Kerman University of Medical Sciences, Iran, Kerman, Iran; 2Endocrine Research Center and Department of Endocrinology Tehran University of Medical Sciences, Tehran, Iran; 3Department of Pulmonary Medicine, Kerman University of Medical Sciences, Kerman, Iran; 4Research Center for Modeling in Health, Kerman University of Medical Sciences, Kerman, Iran; 5Department of Internal Medicine, Kerman University of Medical Sciences, Kerman, Iran.

Background
Exacerbations are an important feature and outcome measure in chronic obstructive pulmonary disease (COPD). The objective of this study was to investigate the effect of supplementation of standard treatment (inhaled long-acting β2 agonists, anticholinergics and corticosteroids) with vitamin D on pulmonary function tests in patients with COPD exacerbation.

Methods
Patients referred to hospital were divided into three groups receiving 0.25 μg calcitriol daily (n = 45), 5000 IU daily of vitamin D (n = 45) and placebo (n = 45). Spirometry and clinical assessment were carried out at the beginning and after 1 week treatment.

Results
There was a similar degree of lung function and clinical improvement in all three groups (P > 0.05). C-reactive protein level did not significantly different among three groups of treatment at 1 week after treatment.

Conclusions
Our findings showed that 1 week supplementation of treatment with 50 000 IU daily of vitamin D or 0.25 μg calcitriol daily did not provide any additional clinical benefit.

DOI: 10.1530/endoabs.32.P116

Lower CD4 lymphocyte counts in HIV/HCV co-infected patients with liver fibrosis on long term HAART and low vitamin D level

Manuel Cayón, Carolina García-Figueros, Patricia Bancalero & Alberto Terrón
1Endocrinology and Nutrition Unit, Hospital SAS, Jerez de la Frontera, Spain; 2Infectious Diseases Unit, Hospital SAS, Jerez de la Frontera, Spain.

Introduction
Vitamin D insufficiency (D-INSUFF) has been associated with impaired immune response in human immunodeficiency virus (HIV) patients and a worse prognosis in patients with liver fibrosis. Nevertheless, few studies have explored the influence of D-INSUFF in immunological response and liver parameters in HIV and hepatitis C virus co-infected patients (HIV/HCV) on long term highly active antiretroviral therapy (HAART) with successful immune and virological response. In this cross-sectional study, first we determined the prevalence of D-INSUFF in a cohort of HIV/HCV outpatients with liver fibrosis and second, we assessed whether the existence of D-INSUFF involves the appearance of relevant immunological data and/or particular clinical aspects related to liver disease.

Methods/design
Thirty-six consecutive HIV/HCV co-infected men (mean age: 48 ± 5.1 years) with liver fibrosis on long term HAART were included in this study. D-INSUFF was defined as 25OH-D levels < 30 ng/ml. Liver fibrosis was defined as the presence of a liver stiffness ≥ 9 kPa measured by FibroScan. Age, data related to HIV and HCV infection, anthropometric, nutritional and metabolic parameters were recorded. Child-Pugh and Model for End-Stage Liver Disease (MELD) were used for assessing the severity of chronic liver disease.

Results
The mean serum 25(OH)-D concentration was 29 ± 11.5 ng/ml with a prevalence of D-INSUFF of 61.1% (mean level: 21.7 ± 4.3 ng/ml). D-INSUFF patients as compared to patients who had normal levels of 25OH-D significantly had lower CD4 lymphocyte count (462.2 ± 170.5/mm3 vs 745.9 ± 107.3/mm3; P = 0.02) and lower serum albumin levels (4.4 ± 0.2 vs 4.8 ± 0.3 g/dl; P = 0.05). Serum PTH, calcium and phosphate levels, liver stiffness value, Child-Pugh and MELD scores were not significantly different among D-INSUFF patients or those with normal 25OH-D level.

Conclusions
Although the level of CD4 lymphocytes is adequate in both groups, the immunological response to HAART is less effective in HIV/HVC co-infected patients with vitamin D insufficiency. Strategies to supplement vitamin D in these patients may help to improve immune status.

DOI: 10.1530/endoabs.32.P117

Changes in anxiety and depression symptoms in patients with chronic fatigue syndrome treated with vitamin D

Anastasia Plescheva, Ekaterina Pigarova & Larisa Dzeranova
Endocrinology Research Centre, Moscow, Russia.

Introduction
Vitamin D is involved not only in the regulation of calcium-phosphorus metabolism; it also plays an important role in maintaining the immune system,
The effects of vitamin D therapy on thyroid functions, thyroid autoantibodies, TNF-α, IL6 and IL1b in patients with autoimmune thyroiditis

Fettah Acibucu1, Hatice Sebila Dokmetas1, Fatih Kiliçli1, Cem Celik2 & Mustafa Aydın2
1Cumhuriyet University Department of Endocrinology and Metabolism, Sivas, Turkey; 2Cumhuriyet University Department of Microbiology, Sivas, Turkey.

Vitamin D has immunomodulatory features and its deficiency is associated with the development of autoimmune diseases. The relation between vitamin D deficiency and autoimmune thyroiditis has not been investigated much. In the present study, our aim was to study the relation between vitamin D therapy and autoimmune thyroiditis. Fifty-four patients having newly diagnosed Hashimoto thyroiditis (HT) and vitamin D deficiency requiring no thyroid hormone replacement therapy at the time of enrollment to the study were included in the study. Once every 3 months, the patients received i.m. cholecalciferol injection (300,000 IU). During diagnosis and at the end of vitamin D therapy, thyroid functions, thyroid antibodies, 25(OH)D3, PTH, Ca, P and ALP levels were in each patient while TNF-α, IL6 and IL1b levels were measured in only 43 patients.

When pretherapy and posttherapy levels of FT4, TSH, antiTPO, antiTG, PTH and ALP were compared, there was a significant difference (P < 0.05). While there was a significant increase in FT4 levels after the therapy, the decrease in TSH, antiTPO, antiTG, PTH and ALP levels was significant. There was no significant difference in terms of FT3, Ca, P, TNF-α, IL6 and IL1b. The was no correlation between pretherapy and posttherapy vitamin D levels and FT4, FT3, TSH, antiTPO, antiTG, PTH, Ca, P, ALP, TNF-α, IL6 and IL1b.

The study included 81 women aged 40–60 years (median age – 53 ± 4 years), 29 of which were diagnosed with the CFS using CDC criteria (1994). Vitamin D levels were evaluated during the period from late June till September by LIASON 25(OH) total vitamin D assay (DiaSorin, Inc.). Beck depression and Zung anxiety scales were completed by patients before and after treatment.

Results
The prevalence of vitamin D deficiency, defined as a level < 20 ng/ml was 54% in patients with CFS and 74% in the control group (P > 0.05), the optimal level of vitamin D (30 ng/ml) was observed in 10 and 14% of patients, respectively (P > 0.05). Medical therapy with cholecalciferol (25 000 IU a week orally during 6 weeks) resulted in decrease in depression scores from 35 to 13 in CFS group (P = 0.00004) and insignificantly from 11 to 9.5 in CFS – group (P > 0.05), decrease in anxiety scores from 38 to 35 in CFS+ group (P = 0.00003) and from 28 to 22 in CFS – (P = 0.000000007); decrease in number of minor diagnostic criteria symptoms in patients with CFS from 5.4 to 4.9 (P = 0.04). The studied parameters did not correlate with levels of vitamin D before and after treatment and with the net change in levels.

Conclusions
There is a high prevalence of vitamin D deficiency in perimenopausal women during period of sufficient insolation irrespective of CFS presence. Vitamin D treatment seems to improve psychological functioning but the mechanisms might not be direct.

DOI: 10.1530/endoabs.32.P119

P121
Genetic analysis of AIP genes in familial primary hyperparathyroidism
Federica Saponaro1, Simona Borsari1, Elena Pardi1, Chiara Banti1, Edda Vignali1, Antonella Meola1, Antonella Picone1, Marco Mastinu2, Stefano Mariotti2, Claudio Marcocci1 & Filomena Cetani1
1Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; 2Endocrinology Unit, Department of Medical Sciences, Policlinico di Monserrato, University of Cagliari, Cagliari, Italy.

Primary hyperparathyroidism (PHPT) is usually a sporadic disorder, but in < 10% of cases occurs as part of hereditary syndromes, including multiple endocrine neoplasia types 1 and 2A (MEN1 and MEN2A), hyperparathyroidism-jaw tumor syndrome (HPT–JT) and familial isolated hyperparathyroidism (FIHP). MEN1 is an autosomal dominant disorder characterized by tumours in multiple endocrine glands, most commonly parathyroid, enteropancreatic and anterior pituitary glands. To date MEN1 gene germline mutations have been identified in 70–80% of MEN1 kindreds. FIHP has a heterogeneous molecular ethiology, since germline mutations of MEN1, HRPT2 and CASR genes have been reported. Germline mutations of the aryl hydrocarbon receptor interacting protein (AIP) gene, responsible for 15–25% of familial isolated pituitary adenoma (FIPA) syndrome, have been recently reported in a MEN1 case.

The aim of this study was to perform a genetic screening of AIP gene in 22 MEN1 and 14 FIHP kindreds. All MEN1 kindreds were negative for MEN1 gene mutations and all FIHP families were negative for MEN1, HRPT2, CASR mutations at genetic testing. Genomic DNA from index cases was analyzed by PCR amplification of the entire coding region and splice sites and direct sequencing by a 16-capillaries automatic sequencer.

Two germline mutations in exon 1 of AIP gene were detected in two MEN1 probands, namely Arg9Gln (c.26G>A) and Arg16His (c.47G>A). Both mutations have already been reported, Arg9Gln in an acromegalic patient, and Arg16His in several FIPA families and patients with apparent sporadic pituitary adenoma. R9Q variant has been described to cause a significant increase in proliferation in cell cultures, while the pathogenetic nature of R16H is still under investigation since it has been identified in few healthy subjects and in some families seems not to segregate with the disease.

Our results suggest that germline AIP mutations may be involved, although rarely, in parathyroid tumorgenesis.

DOI: 10.1530/endoabs.32.P121
P122
A986S or the R990G polymorphism in CASR does not explain hypercalcemia and low normal serum calcium
Anne Qvist Rasmussen1, Niklas Rye Jørgensen1,2, Jacob Tielt-Hansen1, Maurizio Bevilacqua1 & Peter Schwarz1
1Copenhagen Hospital Glostrup, Glostrup, Denmark; 2Luigi Sacco Hospital (Vialba), Milan, Italy; 3Statsen Serum Institut, Copenhagen, Denmark.

The calcium receptor (CASR) serves as one of the main regulators of the calcium homeostasis. CASR is expressed in among other tissues parathyroid chief cells and kidney tubule cells. It has been hypothesized that CASR gene variations are responsible for low circulating calcium levels together with hypercalcemia and thereby increased risk of kidney stones. The CASR gene polymorphism A986S has been shown associated to elevated serum calcium levels in vivo. On the opposite R990G has been shown associated to low serum calcium levels.

Aim
Are the polymorphisms A986S and R990G overrepresented in hypercalcemia patients with low normal serum calcium levels.

Method
The CASR gene was sequenced in 109 Italian out-patient Caucasians suffering hypercalcemia (calcium excretion > 4 mg calcium/day). The patients had low normal serum calcium values and serum PTH within the normal range. All had normal kidney function.

Results
Sixty-eight of 109 patients (62%) showed at least one single-nucleotide polymorphism (SNP). Up to 4 SNP’s were found in each patient, all well characterised. Of these 37 patients (28%) presented A986S, 12 patients (15%) the R990G polymorphism.

Discussion
The observed A986S and R990G distribution corresponds to the frequency and genotypen shown in the ancestry population of Northern and Western European. The A986S or the R990G polymorphism does not explain hypercalcemia and low normal serum calcium in this cohort.

DOI: 10.1530/endoabs.32.P122

P123
Early measure of postoperative iPTH and corrected calcium as predictors of future hypoparathyroidism: which, when and why?
Miguel Paja, Cristina Moreno, Estibaliz Ugarte, Amelia Oleaga, Ma Teresa Gutierrez, Ana J Izuzquiza, Eider Etxeberria, Natalia C Iglesias, Aitzol Lizarra & Maria P Martindez-Mate
Hospital de Basurto, Bilbao, Basque Country, Spain.

Introduction
Intraoperative parathyroid hormone assay (ioPTH) has been validated as a useful tool for predicting postoperative hypocalcaemia (hypoCa) after thyroid surgery and has been proposed as a guide to early discharge from hospital. Its value to predict the risk of future hypoparathyroidism (hypoPT) has not been analyzed in patients with sporadic PHPT compared to the healthy subjects and hypoparathyroid (HypoPT) patients. No data are currently available on Dkk1 serum level in PHPT.

We evaluated serum Dkk1 and serumostatin levels in PHPT patients (16, 9 males and 7 females) compared to HypoPT patients (36, 10 males and 26 females). We have to reach an exact level or timing for its measurement.

Our study confirms the utility of perioperative (PTH) as predictor of postoperative hypoCa and future hypoPT, but we have not found an exact level or timing for its measurement.

DOI: 10.1530/endoabs.32.P124

P124
Serum sclerostin and Dkk1 in patients with parathyroid disorders
Giuseppe Viccica, Simona Borsari, Elena Pardi, Silvia Chiavistelli, Sonia Albertini, Roberta Centoni, Filomena Cetani & Claudio Marconcini
Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy.

The ‘canonical’ Wnt/beta-catenin pathway plays an important role in the development and patterning of bone. Dkk1 (Dickkopf1) and sclerostin are competitive soluble inhibitors of this pathway. Serum sclerostin is decreased in patients with primary hyperparathyroidism (PHPT) compared to the healthy subjects and hypoparathyroid (HypoPT) patients. No data are currently available on Dkk1 serum level in PHPT.

We evaluated serum Dkk1 and serumostatin levels in 42 patients with PHPT (16, 9 males and 7 females) compared to HypoPT patients (36, 10 males and 26 females). We have to reach an exact level or timing for its measurement.

No data are currently available on Dkk1 serum level in PHPT. Serum sclerostin concentration in PHT patients (15.8 ± 7.0 pmol/l) was lower than in controls (20.4 ± 7.9 pmol/l, P = 0.198) and between HypoPT patients and controls (P = 0.382). Serum Dkk1 concentration was lower in PHT (6.2 ± 2.6 pmol/l, P = 0.0001) and HypoPT patients (6.3 ± 2.3 pmol/l, P = 0.0026) compared to healthy subjects (9.2 ± 3.6 pmol/l), whereas no difference was found between PHPT and HypoPT patients (18.4 ± 8.1 pmol/l, P = 0.198) and between HypoPT patients and controls (P = 0.382). Serum Dkk1 concentration was lower in PHT (6.2 ± 2.6 pmol/l, P = 0.0001) and HypoPT patients (6.3 ± 2.3 pmol/l, P = 0.0026) compared to healthy subjects (9.2 ± 3.6 pmol/l), whereas no difference was found between PHPT and HypoPT patients (P = 0.940). In PHT patients, there was a negative correlation between serum PTH and sclerostin (r = –0.342, P = 0.025), and no correlation between PTH and Dkk1 level. No correlation was found between sclerostin, Dkk1 and bone turnover markers, bone density.

In conclusion, serum levels of sclerostin and Dkk1 are decreased in patients with PHPT compared to controls; no definitive conclusion can be reached in patients with HypoPT because of the limited number of patients.

DOI: 10.1530/endoabs.32.P124

P125
An observational study reveals that neonatal vitamin D is primarily determined by maternal contributions: implications of a new assay on the roles of vitamin D forms
Spyridon Karras1, Ilfhat Shah1,2, Andrea Petrocci1,2, Dimitrios Goulis1, Helen Bili1, Fotini Papadopoulou2,2, Panagiotis Anagnostis3, Aggeliki Persinaki1, Basil Tarlatzis1 & Declan Naughton1
1Unit of Reproductive Endocrinology, First Department of Obstetrics and Gynecology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece; 2School of Life Sciences, Kingston University, London, UK; 3Department of Endocrinology, Diabetes and Metabolism, Panagia General Hospital, Thessaloniki, Greece.

Introduction
Intraoperative parathyroid hormone assay (ioPTH) has been validated as a useful tool for predicting postoperative hypocalcaemia (hypoCa) after thyroid surgery and has been proposed as a guide to early discharge from hospital. Its value to predict the risk of future hypoparathyroidism (hypoPT) has not been analyzed in patients with sporadic PHPT compared to the healthy subjects and hypoparathyroid (HypoPT) patients. No data are currently available on Dkk1 serum level in PHPT.

We evaluated serum Dkk1 and serumostatin levels in 42 patients with PHPT (16, 9 males and 7 females) compared to HypoPT patients (36, 10 males and 26 females). We have to reach an exact level or timing for its measurement.

No data are currently available on Dkk1 serum level in PHPT. Serum sclerostin concentration in PHPT patients (15.8 ± 7.0 pmol/l) was lower than in controls (20.4 ± 7.9 pmol/l, P = 0.198) and between HypoPT patients and controls (P = 0.382). Serum Dkk1 concentration was lower in PHPT (6.2 ± 2.6 pmol/l, P = 0.0001) and HypoPT patients (6.3 ± 2.3 pmol/l, P = 0.0026) compared to healthy subjects (9.2 ± 3.6 pmol/l), whereas no difference was found between PHPT and HypoPT patients (18.4 ± 8.1 pmol/l, P = 0.198) and between HypoPT patients and controls (P = 0.382). Serum Dkk1 concentration was lower in PHPT (6.2 ± 2.6 pmol/l, P = 0.0001) and HypoPT patients (6.3 ± 2.3 pmol/l, P = 0.0026) compared to healthy subjects (9.2 ± 3.6 pmol/l), whereas no difference was found between PHPT and HypoPT patients (P = 0.940). In PHPT patients, there was a negative correlation between serum PTH and sclerostin (r = –0.342, P = 0.025), and no correlation between PTH and Dkk1 level. No correlation was found between sclerostin, Dkk1 and bone turnover markers, bone density.

In conclusion, serum levels of sclerostin and Dkk1 are decreased in patients with PHPT compared to controls; no definitive conclusion can be reached in patients with HypoPT because of the limited number of patients.

DOI: 10.1530/endoabs.32.P124

Endocrine Abstracts (2013) Vol 32

>15 pg/ml in 9.5%, all ThyroPPT. Mean (Cat h) was significantly lower in patients who suffered hypoPT (8.63 vs 8.22, P = 0.001). Conclusion

Our study confirms the utility of perioperative (PTH) as predictor of postoperative hypoCa and future hypoPT, but we have not found an exact level or timing for its measurement.

DOI: 10.1530/endoabs.32.P123
Methods
All vitamin D forms were quantified in 60 mother–neonate paired samples by a novel mass spectrometry (LC–MS/MS) assay. Maternal characteristics (age, ultraviolet B exposure, dietary intake, calcium, phosphorus and parathyroid hormone) were recorded. Hierarchical linear regression was used to predict neonatal 25(OH)D concentrations.

Results
Maternal data had similar concentrations of 25(OH)D$_3$ and 25(OH)D$_2$ forms compared to neonates (17.9±13.2 vs 15.9±13.6 ng/ml, P = 0.289) with a ratio of 1:3. The epimer concentrations were similar in mothers and neonates (4.8±7.8 vs 4.5±4.7 ng/ml, P = 0.556). Neonatal 25(OH)D$_2$ was best predicted by maternal characteristics, whereas 25(OH)D$_3$ was strongly associated to maternal vitamin D forms (R$^2$=0.253 vs 0.076 and R$^2$=0.109 vs 0.478, respectively). Maternal characteristics explained 12.2% of the neonatal 25(OH)D$_2$, maternal 25(OH)D$_3$ concentrations explained 32.1%, while epimers contributed an additional 11.9%.

Conclusions
By applying a novel highly specific vitamin D assay, the present study is the first to quantify 3-epi-25(OH)D$_2$ concentrations in mother–newborn pairs. Maternal characteristics and active forms of vitamin D, along with their epimers explain 56% of neonate vitamin D$_3$ concentrations. The roles of active and epimer forms in the maternal–neonatal vitamin D relationship warrant further investigation.

DOI: 10.1530/endoabs.32.P125

**P126**

**Vitamin D and sarcopenia in HIV-infected patients**

Noemi González Pérez de Villar$^1$, Vicente Estrada Pérez$^2$, Jose M Peña Sánchez de Rivera$^1$, Antonio Zapatero Gaviria$^1$, Rosa Villar Vicente$^1$, Gloria Cánovas Molina$^1$, Emilia Cancer Mincho$^1$, Azucena Rodriguez Robles$^1$, M Teresa Martínez Larrad$^1$ & Manuel Serrano Ríos$^1$

$^1$Hospital Universitario de Fuenlabrada, Madrid, Spain; $^2$Hospital Universitario Clínico San Carlos, Madrid, Spain; $^3$Hospital Universitario La Paz, Madrid, Spain.

Introduction
Sarcopenia, an age-associated loss of skeletal muscle mass and function, has been related to higher mortality in general population as well as in HIV-infected patients. In elderly, sarcopenia is a marker of frailty. The aim of our study was to describe the prevalence of sarcopenia and related factors in HIV-infected population.

Methods
Skeletal muscle mass (SMM), total fat mass and body fat distribution were measured by DXA scan. Muscle mass index (MMI) was calculated (lower limit SMM/height$^2$). Sarcopenia was defined as an MMI <2 SD from observed in general population (7.26 kg/m$^2$, 5.5 females). Body fat distribution was determined by body fat index (trunk fat mass/limb fat mass). Plasma levels of 25-OH-vitamin D (VD) were measured by immunoassay.

Results
321 HIV-infected patients were studied. 85% were male, median age was 38 years (IQR 32–45), BMI was 23.8 (IQR 22–26) kg/m$^2$; 45% naive and 54% on ART. 85% were male, median age was 38 years (IQR 32–45), BMI was 23.8 (IQR 22–26) kg/m$^2$; 45% naive and 54% on ART.

**P127**

**Lithium-associated hyperparathyroidism: a case report**

Mafalda Marcelino, João Silva, Luís Lopes, Lucilia Salgado, Carlos Lopes & João Jacome de Castro

Armed Forces University Hospital, Lisbon, Portugal.

Introduction
Lithium therapy is commonly used in bipolar disorder treatment. Alongside the increasing prevalence of goiter and hypothyroidism, the sustaining use of lithium therapy is associated with several metabolic disorders, such as hypercalcemia and hyperparathyroidism (HPT).

Case report
A 64-year-old woman with history of bipolar disorder treated with lithium for several years was referred to our department for evaluation of recurrent hypercalcemia and asymptomatic multinodular goiter (MNG). Euthyroid MNG (benign fine needle biopsy) and a lithium-associated hyperparathyroidism (blood calcium 10.6 mg/dl (8.4–10.2); phosphorus 2.06 mg/dl (2.0–4.0) PTH 256 pg/dl (15–60)) were diagnosed. SestaMIBI scan was negative. A bone mineral densitometry showed reduced T-score in forearm (−2.0).

As lithium therapy was essential and could not be discontinued, we started bisphosphonate therapy (aldronatone 70 mg/week) and conservative management with regular follow-up was planned. After 1 year of follow-up she showed a severe deterioration of the HPT with increasing calcium levels (12.8 mg/dl). A new SestaMIBI scan suggested a left lower parathyroid adenoma (PTA) and was referred to surgery.

A total thyroidectomy and a left lower parathyroidectomy were performed. Histology confirmed a PTA with 13×12×8 mm and a follicular hyperplasia of the thyroid gland, with multinodular goiter. After surgery, the calcium levels normalized and PTH levels decreased. She starts treatment with levothyroxine and maintained lithium therapy.

During 1 year, its calcium levels sustain normal, but PTH levels were mildly increased. She performed another SestaMIBI scan that was negative. She maintains a conservative management with regular follow up in our department.

Discussion
It is still unclear whether lithium-associated HPT causes four-gland hyperplasia or promotes the growth of pre-existing parathyroid adenomas (PTA). This leads to a discussion about what should be the best surgical approach. A four-gland exploration is frequently necessary, but excision of simple adenomas may be a valid option. Patients under lithium therapy should be closely monitored to potential HPT, attempting early diagnosis and avoiding associated comorbidities.

DOI: 10.1530/endoabs.32.P127

**P128**

**Late-onset hypoparathyroidism 15 years after thyroidectomy**

Joana Menezes Nunes, Elisabete Rodrigues & Davide Carvalho

Centro Hospitalar São João, Porto, Portugal.

Introduction
Post-surgical hypoparathyroidism is a well known complication of total thyroidectomy. It may occur as transitory hypoparathyroidism that spontaneously recover within a few weeks/months and as permanent hypoparathyroidism needing long-term treatment. Only few cases of hypoparathyroidism newly diagnosed many years after surgery have been reported. We present a patient with hypoparathyroidism that became clinically evident 15 years after the thyroid surgery.

Case report
Female, 32 years old submitted to total thyroidectomy for papillary thyroid carcinoma (pT2N1M0) in 1998 at another institution. She was referred to our consultation in September/09 for follow-up and remained clinically asymptomatic until March/12, when she was observed in the Emergency Department due to complaints of hand paresthesias and carpal spasm. Severe hypocalcemia (Ca = 5.4 mg/dl (8.8–10.6), Ca$^{2+}$ = 0.68 mg/dl (1.15–1.35)) was diagnosed. She was treated with i.v. calcium gluconate and after resolution of signs and symptoms was discharged on calcitriol, calcium carbonate and cholecalciferol therapy. Due to constipation, she abandoned her own initiation calcitriol a month later. The analytical study of calcium metabolism revealed postsurgical hypoparathyroidism (PTH = 10.2 pg/ml (10.0–65.0), Ca = 4.1 mg/dl (4.2–5.1), Ca$^{2+}$ = 2.04 mmol/l (2.26–2.64), PO4$^{3-}$ = 4.6 mg/dl (2.7–4.5), Mg$^{2+}$ = 1.50 mmol/l (1.55–2.05)). The patient is now asymptomatic on supplementation with calcitriol, calcium and cholecalciferol.
Conclusion
Late-onset hypoparathyroidism appearing years after total thyroidectomy is a rare condition. Symptoms of hypocalcemia may be latent and subtle (such as weakness, tiredness, irritability and depression) and thus attributed to other diseases. Although hypocalcemia typically occur after surgery, progressive atrophy of the parathyroid glands, leading to its insufficiency years after thyroid surgery, may result in a late latent hypocalcemia. Although we lack data on radioactive iodine (I131) therapy and she is not able to ensure that information, it is another possible factor contributing to late hypoparathyroidism.

DOI: 10.1530/endoabs.32.P128

P129
Does recognition of vitamin D deficiency affect the indication for surgical treatment in asymptomatic primary hyperparathyroidism?
Laura Gianotti, Francesco Tassone, Micaela Pellegrino, Claudia Balfoni, Sara Cassibba, Gianpaolo Magro, Flora Cesario & Giorgio Borretta
S. Croce and Carle Hospital, Cuneo, Italy.

Introduction
Current guidelines for the management of asymptomatic primary hyperparathyroidism (A-pHPT) recommend that 25-hydroxyvitamin D levels should be assessed in all patients and vitamin D deficiency (VDD) should be cautiously considered. It is unknown whether VDD affects the probability to meet surgical criteria currently proposed for A-pHPT. Aim of study was to evaluate whether VDD recognition affects the probability to meet surgical criteria in A-pHPT patients.

Methods
Eighty consecutive A-pHPT patients were studied (mean ± s.d. age: 66.5 ± 8.9 years; male/female = 10/70; PTH: 179.8 ± 134.7 ng/l; calcium: 10.8 ± 0.7 mg/dl; ionized calcium: 1.39 ± 0.10 mmol/l; 25OHDI: 30.0 ± 21.3 ng/ml). VDD was defined as 25-hydroxyvitamin D ≤20 ng/ml. The criteria for surgery of III International Workshop on the Management of A-pHPT were considered, i.e.: Serum calcium ≥1 mg/dl the upper normal limit; creatinine clearance < 60 ml/min; T-score <-2.5 at any site.

Results
VDD was present in 32 patients (40%). A-pHPT patients with VDD showed higher PTH (P = 0.0007), total (P = 0.04) and ionized calcium (P = 0.013) and lower forearm T-score (P = 0.019) compared with A-pHPT without VDD. No difference in fulfillment of any surgical criteria was present between A-pHPT patients with or without VDD (calcium criterion = 25 vs 25, P = 0.258; eGFR criterion = 19.4 vs 21.7%, P = 1.00; T-score criterion = 78.1 vs 64.6%, P = 0.2226, respectively).

Conclusion
VDD is not rarely detected in A-pHPT and affects biochemical and densitometric features; however, the recognition of VDD does not affect the probability to meet surgical criteria proposed by current guidelines in A-pHPT. Thus, the assessment of vitamin D status, as recommended, does not affect the therapeutical choice for surgery in A-pHPT.

DOI: 10.1530/endoabs.32.P129

P130
Fahr’s disease with dystonia: a case report
Berna Imge Aydogan, Ugur Unlüütürk, Ferda Can, Mustafa Sahin & Ali Riza Uysal
Department of Endocrinology and Metabolism Diseases, Ankara University Faculty of Medicine, Ankara, Turkey.

Background
Fahr’s disease is a rare degenerative disorder characterized by symmetrical and bilateral intracranial calcification. Movement disorders are the most common symptoms of Fahr’s disease and dystonia is an uncommon presentation which accounts for only 8% of symptomatic patients.

Case report
A 47 years old female admitted to emergency department with involuntary movements of extremities and anxiety. Neurological examination was normal except repetitive contractions and involuntary movements mainly on left arm and leg. In her medical history subtotal thyroidectomy was performed for multinodular goiter 28 years ago. There was no family history of neurological disease. She was consulted by neurology for insomnia and anxiety 5 years ago. Valproic acid and haloperidol were given with the diagnosis of epislepsia and insomnia. She has had involuntmary movements for 2 years which worsened during the last 2 months and her life quality decreased rapidly. Her symptoms considered to be the side effect of haloperidol treatment and drug was stopped, but no improvement was observed after the discontinuation of haloperidol. On the laboratory, serum calcium was 6.8 mg/dl (normal 8.4–10.6 mg/dl), phosphate 4.8 mg/dl (normal 2.3–4.7 mg/dl), albumin: 4.1 mg/dl, parathormone was 0.25 pg/ml (normal 15–65 pg/ml). EMG showed 400–500 ms non-rhythmic bursts which is typical for dystonia. Cranial CT revealed massive calcifications involving basal ganglia, thalamus and cerebellar nuclei. The results supported the diagnosis of Fahr’s disease caused by hypoparathyroidism. Serum calcium level was increased to acceptable range after calcitrol and calcium carbonate treatment and resulted in complete resolution of dystonia.

Conclusions
We present a case of Fahr’s disease caused by longstanding hypoparathyroidism and manifested with dystonia, an unusual presentation of disease. Though it is rare, it is important to remember that hypoparathyroidism can be the cause of Fahr’s disease accompanied by unusual neurological disorders.

DOI: 10.1530/endoabs.32.P130

P131
Predictive factors of postoperative hypoparathyroidism after total thyroidectomy
Miguel Paja, Eider Etxeberria, Laura Calles, Amaia Expósito, Estibaliz Ugarte, Cristina Moreno, Aitzol Lizarraga, Javier Espiga & Amelia Oleaga
Hospital de Basurto, Bilbao, Basque Country, Spain.

Introduction
Hypoparathyroidism (hypoPT) is the most frequent complication after thyroid surgery, usually as transient hypocalcaemia. Permanent parathyroid lesion is less frequent, but it can extend hospital stay and complicate postoperative management. Several preoperative factors predicting the development of hypoPT have been identified, including advanced age, hyperthyroidism, surgical experience and others. We evaluate the role of some potentially predictive factors in our recent surgical series.

Description of methods/design
We analyze retrospectively 649 patients with total thyroidectomy from 2005 to 2011, followed up more than 1 year after surgery. Permanent hypoPT (PhypoPT) is defined by (iPTH) <15 pg/ml without treatment more than 1 year after surgery. (iPTH) between 5 and 15 pg/ml were defined as partial deficiency, whereas <5 pg/ml was considered total deficiency. Cases with spontaneous recovering of parathyroid function after a period of (PTh): <15 were named as transient hypoPT (ThypoPT). We consider age, thyroid size (by weight), sex, presence of hyperthyroidism, central dissection and cause of surgery as variables in our study.

Results
449 patients didn’t show postoperative hypoPT (70.6%), 151ThypoPT (23.3%; 87 of them normalized at 1st month) and 49 (7.5%) PhypoPT, 27 of them (4.1%) total deficiency. Significant differences among the three groups were found in three variables: thyroid weight, lower in PhypoPT (mean ( S.D.): 53.5 (57.8) g vs 8.9 (7.0) g, P < 0.027); fulfillment of central dissection, carrying an OR for hypoPT of 5.06 (CI: 3.10–8.28), and OR for PhypoPT vs ThypoPT: 3.08 (CI: 1.99–4.77); and surgery reason (cytology/biopsy vs others; OR for HypoPT: 1.72 (CI: 1.22–2.41), and OR for PhypoPT vs ThypoPT: 1.38 (CI: 1.04–1.84)). Neither age nor prevalence of hyperthyroidism showed differences among three groups as well as sex distribution.

Conclusion
Parathyroid damage is more prevalent in total thyroidectomy when it is indicated for malignant or suspicious cytology or biopsy, particularly when it is completed with dissection of central cervical compartment in smaller glands. Our series finds that gender, age or hyperthyroidism haven’t got influence in the risk of postoperative hypoPT.

DOI: 10.1530/endoabs.32.P131
P132

Normocalcemic primary hyperparathyroidism: an Italian epidemiologic study

Edda Vignali1, Antonella Meola1, Roberta Centoni1, Gibilaro Rosa Maria1, Giuseppe Dianzani2, Filomena Cetani1, Silvia Chiaivitelli1, Federica Saponaro1 & Claudio Marcocci1

1Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; 2Laboratory of Clinical Chemistry, University Hospital of Pisa, Pisa, Italy.

Primary hyperparathyroidism (PHPT) is defined by hypercalcemia and high PTH levels. In recent years a variant of PHPT has been described, namely normocalcemic PHPT (NPHT), which is characterized by normal serum calcium and high PTH levels, in the absence of other causes of secondary hyperparathyroidism. The epidemiology of NPHT is poorly understood. We performed a survey in the early fall in a small Southern Italian village, in which all adult residents (n = 1811) were invited to participate. A total of 1056 accepted to participate and blood samples were collected for measurement of serum calcium, albumin, creatinine, PTH and 25OH-D. Daily calcium intake was also evaluated using a self-administered questionnaire. A complete set of results was available in 679 subjects (age 18–89 years; 422 F and 257 M). Four women (0.6%) had PHPT. Two hundred and eighty-eight individuals (42.4%) had high PTH (nl: 10–65 pg/ml) and normal albumin-adjusted serum calcium (aCa; nl: 8.6–10.2 mg/dl). Two hundred and sixty-three of them were excluded because of serum 25OHD < 30 ng/ml (n = 241, 83.7%) or eGFR < 60 ml/min per 1.73 m² (n = 22, 7.6%). NPHT was identified in the remaining 25 subjects (11 F; mean age 47 years, 5 postmenopausal) and 14 M (mean age 47 years), with an overall prevalence of 0.5% (3.5%). PTH, aCa and 25OHD (mean ± s.d.) concentrations were 89.0±21.5 pg/ml, 9.0±0.3 mg/dl, and 37.6±7.2 ng/ml, respectively. No relationship was found between PTH and quartile of daily calcium intake. In conclusion, the association of high PTH and normal aCa is rather a common finding, and in the majority of cases is linked to low 25OHD levels and less frequently to renal failure. However, a definite proportion of subjects (3.5%) met the criteria of NPHT. Longitudinal studies in the latter subjects is needed to establish whether NPHT represents an early stage of classical PHPT or a separate entity.

DOI: 10.1530/endoabs.32.P132

P133

Plasma lipid levels in relation to the status of vitamin D sufficiency

Inmaculada Gonzalez-Molero, Gemma Rojo, Marta Dominguez, Sonsoles Morcillo, Eleazara Rubio, Carla Gutierrez, Marisol Riés de Adana, Maria Cruz Almaraz & Federico Soriguer

Carlos Haya Hospital, Endocrinology Service, Malaga, Spain.

Introduction

Several studies have investigated a possible action of vitamin D metabolites on different lipid fractions but the possible mechanism by which they could act remain unknown, with varying results in observational and intervention studies.

Objective

To study the relation between vitamin D levels and lipid levels.

Methods

We undertook a population-based cohort study in Spain. At baseline (1996–1998), 1226 subjects were evaluated. Follow-up visits were performed in 2002–2004 and 2005–2007. At baseline and follow-up, participants underwent an interview and a standardized clinical examination. At the second visit, 25-hydroxyvitamin D levels and 25OHD levels were measured. To evaluate the association between dyslipidemia and 25-hydroxyvitamin D levels, the odds ratio (OR) and 95% CI were calculated using a logistic regression model. In all cases the level of rejection of a null hypothesis was a = 0.05.

Results

The mean levels of total cholesterol (TC) in second study were: 249.73±51.05, triglycerides: 113.18±73.21, HDL: 66.35±16.38 and LDL:161.6±46.71 mg/dl. In the third study, levels were 201.61±38.11, 116.61±78.60, 54.78±12.98 and 123.58±23.12 mg/dl. Mean levels of different lipid fractions in the second study depending on the presence or absence of vitamin D deficiency were: TC: 256.68±51.91 vs 246.07±53.37 (P = 0.006), triglycerides: 87.53±119.94 vs 106.34±63.82 (P = 0.01), HDL: 68.47±17.5 vs 65.24±16.57 (P = 0.007), LDL: 120.91±30.76 vs 108.45±25.05 (P = 0.01); ratio TC/HDL: 3.90±0.96 vs 3.90±0.98 (P = 0.9); ratio LDL/HDL: 1.69±0.51 vs 1.67±0.53 (P = 0.7). The mean levels of 25-hydroxyvitamin D were significantly lower in subjects with high TC (22.5 vs 24.2 ng/ml), high HDL (22.1 vs 23.2 ng/ml) and triglycerides (21.1 vs 23.2 ng/ml). No correlation was found between CT and 25-hydroxyvitamin D (r = −0.06, P = 0.08), but there was a negative correlation with HDL and TG (r = −0.07, P = 0.03 and r = −0.09, P = 0.01) adjusted for age, sex and weight. In the cross-sectional study in the multivariate model we didn’t obtained relationship between vitamin D deficiency (< 20 ng/ml) and elevated total cholesterol (OR = 0.85, 95% CI: 0.57–1.28) or low HDL (OR = 1.42, 95% CI: 0.75–2.71) after adjustment for age, sex and obesity, but the relationship between vitamin D deficiency and hypertriglyceridemia persisted, so that subjects with deficit of vitamin D were more likely to have high triglycerides (OR = 0.68, 95% CI: 0.47–0.98, P = 0.03). In the prospective study, after 4 years of follow up, patients with or without vitamin D deficit, had similar risk of hypertriglyceridemia adjusted by age, sex and presence of obesity (OR: 1.01, P = 0.95). No relationship was found with other lipid fractions in prospective study.

Conclusion

Vitamin D deficiency is not associated with increased prevalence of hypertriglyceridemia.

Vitamin D deficiency is not related to the incidence of dyslipidemia.

DOI: 10.1530/endoabs.32.P133

P134

Primary hyperparathyroidism and vitamin D deficiency, therapeutic implications

Ifigenia Kostoglou-Thanassiou1, Panagiotis Thanassiou2, Anastasios Gkountouvas3, Eleni Xanthakou4, Ioannis Keramidas5, Fotini Chatjimarkou1 & Philipppos Kalrymids6

1Department of Endocrinology, Red Cross Hospital, Athens, Greece; 2Department of Rheumatology, St Paul’s Hospital, Thessaloniki, Greece; 3Department of Endocrinology, Metaxa Hospital, Pireaus, Greece; 4Endocrinologist, Athens, Greece.

Primary hyperparathyroidism is a rather frequent disorder characterized by high plasma PTH and calcium. Vitamin D deficiency is prevalent in all areas of the world. Vitamin D deficiency has been described in patients with primary hyperparathyroidism. When present, vitamin D deficiency may be associated with large size parathyroid adenomas and musculoskeletal pain.

The aim was to describe two cases of primary hyperparathyroidism and vitamin D deficiency.

A patient, male aged 87 years, was hospitalized for coronary insufficiency and diffuse musculoskeletal pain. During hospitalization high plasma calcium was observed, calcium levels being 10.5 mg/dl. Laboratory investigations revealed high plasma parathyroid hormone levels, PTH being 117 pg/ml (normal values 10–65 pg/ml) and low plasma 25(OH)D levels, 25(OH)D being 8 ng/ml (normal values <30 ng/ml). Bone mineral density was measured in the neck of the left femur and revealed a T-score of −3.05. Vitamin D supplementation was initiated followed by the administration of alendronate. Ultrasoundography revealed an adenoma beneath the right lobe of the thyroid gland. Conservative management was chosen due to old age. A patient, female aged 42 years, presented with diffuse musculoskeletal pain. Laboratory investigations revealed high plasma PTH (PTH 163 pg/ml), low plasma 25(OH)D (25(OH)D <9 ng/ml) and calcium 11.3 mg/dl.

On scintigraphy a parathyroid adenoma was visualized beneath the left lobe of the thyroid gland. Vitamin D supplementation was performed following surgery to remove the parathyroid adenoma. Postoperatively, the patient developed hungry bone syndrome. In both cases after vitamin D supplementation the diffuse musculoskeletal symptoms improved.

Conclusions

Vitamin D deficiency may be found in the context of primary hyperparathyroidism. When present, vitamin D supplementation should be initiated cautiously, as it may aggravate primary hyperparathyroidism. Cautious vitamin D supplementation is however necessary, will not cause an increase in calcium and PTH levels and will improve musculoskeletal pain.

DOI: 10.1530/endoabs.32.P134

Endocrine Abstracts (2013) Vol 32
**P135**

**Prevalence and correlates of vitamin D deficiency in Turkish adults**

Ilhan Saltman1, Nese Ozboy1, Harika Boztepe1, Sibel Kalaca2, Beyhan Omer1, Refik Tanakol1, Yildiz Tutuncu1, Semra Genc1 & Faruk Alagoz1

1Istanbul University Istanbul Faculty of Medicine, Istanbul, Turkey; 2Marmara University Faculty of Medicine, Istanbul, Turkey.

Enormous evidence suggests that vitamin D deficiency could be linked to several chronic diseases, including cardiovascular disease, diabetes, obesity, depression and cancer. The purpose of this study was to examine the prevalence of vitamin D deficiency and its correlates to test the hypothesis that vitamin D deficiency was common among adult Turkish population, particularly in women. The Turkish Diabetes, Hypertension, Obesity and Endocrine Disease Survey (TURDEP-II) Jan to June 2010 data were analyzed for vitamin D levels in adult participants (n = 9560, mean ± s.d.) age: 45.3 ± 15.4 years, 64% women. Serum 25(OH)D was inversely correlated with PTH (r = -0.122, P < 0.001). Serum 25(OH)D levels (controlled for age, gender, region, living environment, BMI, waist, and season) correlated with fish, cheese, and sunflower oil consumption; serum levels of creatinine, HDL-cholesterol, FTA, vitamin B12, folates, IGFI, IGFBP3 and eGFR.

Vitamin D deficiency was defined as 25(OH)D concentrations ≤ 20 ng/ml (≤ 50 nmol/l). The overall prevalence rate of vitamin D deficiency was 93%, with the highest rate seen in younger (<40 years) age group (96.2%) in women, and elderly (≥65 years) age group (91.9%) in men. Multiple logistic regression model with Z scores showed that male gender, increase in total cholesterol (39.3 mg/dl), HDL-cholesterol (12.3 mg/dl) and IGFI levels (69.0 ng/ml) positively associated; but eGFR (18.6 ml/min) and PTH (22.7 pg/ml) levels inversely associated with vitamin D (≥20 ng/ml).

In conclusion, vitamin D deficiency was common among adult Turkish population, particularly in child-bearing age women. Given that vitamin D deficiency is linked to important risk factors of leading cause of morbidity and mortality in Turkey, it is important that health professionals should be aware of this connection and health authorities arrange intervention strategies, such as vitamin D fortification of foods to correct vitamin D deficiency at the population level.

DOI: 10.1530/endoabs.32.P135

**P136**

**Vitamin D deficiency in urban adult population of south-eastern Poland**

Małgorzata Trofimiuk-Muldner, Małgorzata Kiec-Klimczak & Alicja Hubalewska-Dydejczyk

Department of Endocrinology, Medical College, Jagiellonian University, Krakow, Poland.

Vitamin D deficiency has been recognized as a common public health issue in many countries, however its prevalence and impact on calcium metabolism parameters has not been extensively studied in Poland yet. The aim of the study was to assess the vitamin D status in sample of Polish urban population. Material and methods: Study included 273 healthy volunteers (76 males, 197 females, median age 58 years) living in city Krakow in south-eastern part of Poland. 56% of them were 65 years) age group (91.9%) in men. Multiple logistic regression model with Z scores showed that male gender, increase in total cholesterol (39.3 mg/dl), HDL-cholesterol (12.3 mg/dl) and IGFI levels (69.0 ng/ml) positively associated; but eGFR (18.6 ml/min) and PTH (22.7 pg/ml) levels inversely associated with vitamin D (≥20 ng/ml).

In conclusion, vitamin D deficiency was common among adult Turkish population, particularly in child-bearing age women. Given that vitamin D deficiency is linked to important risk factors of leading cause of morbidity and mortality in Turkey, it is important that health professionals should be aware of this connection and health authorities arrange intervention strategies, such as vitamin D fortification of foods to correct vitamin D deficiency at the population level. Statistical analysis was performed by ANOVA, with post-hoc test Bonferroni.

**Results**

Bone fractures, BMD and vitamin D levels differ among the groups significantly (P < 0.05). The highest frequency of bone fractures was observed in patients with lactose intolerance and previously diagnosed hyperlipidaemia (0.84/patient) which was accompanied by the lowest 25OH vitamin D level (26.08 ± 9.25 nmol/l) and bone mineral density in femoral neck region (Zsc: −1.29 ± 0.21).

**Conclusion**

The recognition of lactose intolerance in time, special attention for associated comorbidities (e.g. lactose intolerance with hyperlipidaemia) and choosing the proper treatment (e.g. sufficient supplementation of vitamin D) should become part of the osteological and fracture prevention of women in fertile age.

DOI: 10.1530/endoabs.32.P136

**P137**

**The effects of lactose intolerance and lactose intolerance associated diseases on serum vitamin D levels, bone metabolism markers, bone mineral density and bone fractures**

Enikee Csoeur1, Bence Acz2,3,4, Orsolya Acz2,3,4, Viktoria Ference4, Szilvia Meszaros5, Edit Toth5, Gabor Farkas5 & Csaba Horvath6

1The Health Service of Budavari Local Authorities, Endocrinology, Budapest, Hungary; 2Semmelweis University School of Ph.D. Studies, Budapest, Hungary; 32nd Department of Internal Medicine, Semmelweis University, Budapest, Hungary; 41st Department of Internal Medicine, Semmelweis University, Budapest, Hungary; 5Department of Rheumatology, County Hospital Flor Ferenc, Kistarcsa, Hungary; 6Centrum-Lab. K.F., Budapest, Hungary.

**Introduction**

Lactose intolerance itself is linked with lower peak bone mass (PBM) and with decreased bone mineral density (BMD) which may decrease further with lactose intolerance associated comorbidities. The aim of our study was to examine how bone metabolic parameters are affected (change of bone metabolism markers, BMD and frequency of fractures) in lactose intolerance which was accompanied by previously diagnosed hyperlipidaemia or by hyperthyroidism.

**Description of methods**

Forty-three female patients (34.88 ± 4.4 years) with lactose intolerance were divided into three groups: n = 16 female patients (32.8 ± 4.4 years) with lactose intolerance only (1), n = 13 female patients (35.6 ± 4.2 years) with lactose intolerance and previously diagnosed hyperlipidaemia (2) and n = 14 female patients (36.5 ± 2.9 years) with lactose intolerance and treated hyperthyroidism (3). BMD was measured by dual-energy X-ray absorptiometry (DEXA) at the one third of distal radius, the femoral neck and the lumbar spine region (L2-L4). Laboratory analysis included routine and also calcium metabolism parameters such as: 25-hydroxyvitamin D (25-OH D), parathyroid hormone (PTH), β-CrossLaps, 25-OH D, vitamin D, osteocalcin (OC). Also prevalence of fractures was recorded. Statistical analysis was performed by ANOVA, with post hoc test Bonferroni.

**Results**

Bone fractures, BMD and vitamin D levels differ among the groups significantly (P < 0.05). The highest frequency of bone fractures was observed in patients with lactose intolerance and previously diagnosed hyperlipidaemia (0.84/patient) which was accompanied by the lowest 25OH vitamin D level (26.08 ± 9.25 nmol/l) and bone mineral density in femoral neck region (Zsc: −1.29 ± 0.21).

**Conclusion**

The recognition of lactose intolerance in time, special attention for associated comorbidities (e.g. lactose intolerance with hyperlipidaemia) and choosing the proper treatment (e.g. sufficient supplementation of vitamin D) should become part of the osteological and fracture prevention of women in fertile age.

DOI: 10.1530/endoabs.32.P137

**P138**

**Normocalcemic hyperparathyroidism**

Mourad Kesraoui, Said Azzoug, Lydia Lounis, Nassima Belhadj Aissa & Farida Chentli

Department of Endocrine and Metabolic Diseases, Bab Oued Hospital, Algiers, Algeria.

**Introduction**

In the whole world normocalcemic hyperparathyroidism (NC HPT) is an emerging entity and a growing problem. This disease is characterized by high levels of intact parathyroid hormone with normal total or ionized serum calcium. Our aim is to analyze its clinical and biological profile and its etiologies.

**Subjects and methods**

We have studied 18 subjects with NC HPT. They all had routine analyses, plasma calcium and phosphorous, and assessment of parathyroid hormone (PTH) and vitamin D. kidney and bone explorations were done too.

**Results**

**Discussion**

NC HPT is considered as a rare clinical presentation, and only few cases have been reported worldwide. NC HPT is characterized by high PTH and normal serum calcium. Plasma levels of calcium and PTH were significantly higher in NC HPT group compared to control group (P < 0.05).

**Conclusion**

NC HPT is an emerging entity and a growing problem. High levels of intact PTH should be kept in mind, and further studies are needed for a better understanding of this entity.
Results
In this group, 16 were females (88.8%) and 2 were males. Their mean age was equal to 51.2 years (36–70), their mean plasma calcium = 9.5 mg/l, mean phosphorus = 32 mg/l, mean PTH = 223 pg/ml (≤ 60). The consultation motive was bone problems in 33.3%. Bone mineral density was low or very low in 14 (77.7%). Recurrent kidney stones were observed in three cases = 16.6%, renal insufficiency = 0%. For etiologies NCHPT was due to vitamin deficiencies in 57.1% and to primitive hyperparathyroidism in 42.9%.

Discussion
As in classical HPT, NC HPT is prevailing in female cases. In NC HPT bone lesions are more frequent than kidney problems. For etiologies, vitamin D deficiency is slightly more frequent than idiopathic primary HPT, but large series are necessary to confirm our results.

DOI: 10.1530/endoabs.32.P138

P139
Familial hypocalciuric hypercalcemia a rare cause of hypercalcemia
Sandra Belo1,2, Angela Magalhães3, João Capela2 & Davide Carvalho1,3
1Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar de São João, Porto, Portugal; 2Department of Endocrine Surgery, Centro Hospitalar de São João, Porto, Portugal; 3Faculty of Medicine, University of Porto, Porto, Portugal.

Introduction
Familial hypocalciuric hypercalcemia (FHH) is caused by inactivating autosomal dominant mutations with high penetrance of CaSP gene. Contrary to severe neonatal hyperparathyroidism, caused by homozygous inactivation of the gene, familial hypocalciuric hypercalcemia is usually associated with inactivating variants in heterozygote.

Case
Male patient, 73 years, with history of Behče’s disease and pulmonary sarcoidosis, was referred for evaluation of hypopituitarism. During the evaluation phospho-calcium metabolism abnormalities were detected: calcium 5.5 mg/dl (4.05–5.2), ionized calcium 2.88 mg/dl (2.26–2.64) inorganic phosphorous 2.8 mg/dl (2.7–4.5), magnesium 1.86 mg/dl (1.55–2.05), confirmed in further studies, intact PTH of 88.9 pg/ml (10.0–65.0), with subsequent normal values. Urinary calcium to creatinine ratio was 0.004 (urinary calcium 2.2 mg/24 h; plasma creatinine 1.3 mg/dl; urinary creatinine 1164 mg/24 h). Parathyroid ultrasound and scintigraphy revealed no changes as well as bone densitometry. The high calcium, the inappropriate high normal intact PTH levels and the low urinary calcium, associated to the absence of symptoms of hyperparathyroidism, prompted us to consider the diagnosis of FHH and to request genetic study. It revealed the presence, in heterozygote, of the pathogenic mutation c.131C>A (p.Cys437X), in exon 4, of CaSR gene. Study of descendents and siblings was recommended, stressing the benign nature of this entity.

Discussion
Familial hypocalciuric hypercalcemia is usually asymptomatic and characterized by mild to moderate hypercalcemia, relative hypocalciuria, normal intact PTH, which can be mildly elevated in 20% of the cases, and high-normal levels of magnesium. Urinary calcium to creatinine ratio <0.01 is found in ~80% of individuals with FHH, while a similar proportion of cases of primary hyperparathyroidism have levels higher than this. FHH is a benign entity and usually does not require treatment. The importance of diagnose and screening is due to the need of differential diagnoses, especially with primary hyperparathyroidism, in order to avoid unnecessary therapeutic interventions.

DOI: 10.1530/endoabs.32.P139

P140
Vitamin D deficiency in lithuanian school graduates females
Lina Zabuliene1,2, Jurgita Urbioniene3, Gitana Skendelyte4 & Svajunas Barakauskas4
1Clinics of Rheumatology, Traumatology-Orthopedics and Reconstructive Surgery, Faculty of Medicine, Vilnius University, Vilnius, Lithuania; 2Antakalnio Out-patient Clinic, Vilnius, Lithuania; 3Infectious Diseases and Tuberculosis Hospital, Vilnius University Hospital ‘Santariskiu klinikos’, Vilnius, Lithuania; 4Public Agency Laboratory ‘Medicina Practica’, Vilnius, Lithuania.

Background
There are evidences that young adults are at risk for poor vitamin D nutritional status. The objective of this study was to investigate the level of vitamin D in school graduates females and the factors associated with vitamin D status.

Material and methods
School graduates females from three Lithuanian cities were enrolled into the project from March to June of 2012. General health, nutrition, physical activity status was assessed by questionnaires. Height, body mass were measured. Blood samples were taken for complete blood count and 25(OH)D. Information on average number of sunshine hours every month in particular city was obtained from the meteorological service.

Results
The study included 287 young adult females. Mean age was 18.33 ± 0.62 years, mean BMI 21.09 ± 1.29 kg/m². 85 females used solarium. Their 25(OH)D level was 22.29 ± 7.42 ng/ml, significantly higher than those who has not used solarium. Data of females using solarium have been excluded from further analysis.

Mean 25(OH)D concentration in 202 subjects was 15.72 ± 7.17 ng/ml. The prevalence of vitamin D deficiency (serum 25(OH)D < 20 ng/ml) was 73.8%. 22.8% of females were found to be vitamin D insufficient (25(OH)D level 20–30 ng/ml) and only 3.4% young adult females were vitamin D sufficient. There were no differences in time spent outdoors, sleep, rest and physical activity hours, meat, fish and milk consumption between groups according to vitamin D status.

Regression analysis showed significant 25(OH)D level and sunshine hours relationship (R² = 0.26, P < 0.0001). Mean 25(OH)D level in April was 13.71 ± 6.10 ng/ml, in May 18.74 ± 6.72 ng/ml and in June 22.27 ± 8.67 ng/ml (P < 0.0001). Regression analysis revealed relationship between 25(OH)D level and white blood cells count (B = 0.921, P = 0.003) and platelets levels (R = −0.020, P = 0.028).

Conclusions
Vitamin D deficiency and insufficiency are highly prevalent in school graduates females. Sunshine exposure is the main source of vitamin D. WBC count increase, if vitamin D level increases.

DOI: 10.1530/endoabs.32.P140

P141
Does vitamin D status predict handgrip strength in young adult women?
Ibrahim Sahin1, Salih Sezgin2, Lezcan Keskin1, Çagatay Taskapan2, Dilek Yavuz3, Selma Aydin Felek4, Zuhal Karaca1 & Hulya Taskapan4
1Inonu University, Endocrinology, Malatya, Turkey; 2Inonu University, Biochemistry, Malatya, Turkey; 3Marmara University, Endocrinology, Istanbul, Turkey; 4Public Health, Malatya, Turkey; 5Inonu University, Internal Medicine, Malatya, Turkey.

Introduction
Increasing evidence suggesting an integral role of vitamin D in skeletal muscle function. The relationship between muscle strength and vitamin D status has been investigated to some degree in older populations, however there has been very little research in younger adult women. This study aims to measure the effects of vitamin D on handgrip strength in young adult women.

Method
A total of 141 healthy women with mean age of 33.8 ± 6.8 were included in this cross-sectional study. Vitamin D, calcium (Ca), phosphorus (P) and parathormon (PTH) levels were measured. Dominant and non-dominant hand-grip strength were measured with hand-grip dynamometer for three times. To minimize seasonal variations all measurements were taken in the March. Ethical committee approved the study protocol.

Results
Mean vitamin D levels and mean handgrip strength were 19.5 ± 2.96 ng/ml and 32.6 ± 5.7 kg respectively. There was no significant difference between the mean handgrip strength of women with vitamin D deficiency (31.9 ± 5.2 kg) or vitamin insufficiency (32.3 ± 5.9 kg) and women with normal vitamin D levels (32.2 ± 6.6 kg). In correlation analysis; there was no significant relation between the mean handgrip strength and the vitamin D, Ca, P levels. There was weak, but significant correlation between the PTH levels and mean handgrip strength (r = 0.174; P = 0.049).

Conclusions
Our results suggest that vitamin D status does not predict handgrip strength at least in young adult women.

DOI: 10.1530/endoabs.32.P141
## Influence of preoperative characteristics in the result of Tc99m-sestamibi scan in patients with primary hyperparathyroidism

### Nerea Egan˜a1, Aitzol Lizarraga2, Miguel Paja2 & Ramon Elorza2

1Hospital Donostia, San Sebastian, Spain; 2Hospital Basurto, Bilbao, Spain.

### Materials and methods

A series of 196 patients with PHP who underwent parathyroidectomy from 1995 to 2012 was included and divided into two groups: positive MIBI and negative MIBI. Positive value was defined when the pathologic gland was correctly localized and negative value when discordant result or no gland was localized.

### Results

<table>
<thead>
<tr>
<th>MIBI+ (124 cases)</th>
<th>MIBI− (72 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 64 (33–84)</td>
<td>63 (21–84)</td>
</tr>
<tr>
<td>Female/male</td>
<td>77.4/22.6%</td>
</tr>
<tr>
<td>Nephrolithiasis</td>
<td>40.3%</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>25.8%</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>22.6%</td>
</tr>
</tbody>
</table>

*P < 0.05.

### Conclusion

This retrospective study shows that there is no influence of biochemical parameters, gland size or tumoral weight in the accuracy of MIBI scintigraphy. We also demonstrate the negative effect of simultaneous thyroid disease in this diagnostic technique. More studies are needed to evaluate the influence of other parameters, like cell type, in accuracy of MIBI scan in parathyroid adenomas.

DOI: 10.1530/endoabs.32.P142

## Cystic parathyroid adenomas: ultrasonography features

### Basak Karbek, Melia Karakise, Mustafa Caliskan, Nujen Colak Bozkurt, Muyesser Sayik Aslan & Tuncay Delibasi

Endocrinology, Diskapi Yildirim Beyazit Teaching and Research Hospital, Ankara, Turkey.

### Introduction

Parathyroid adenomas appear typically as homogeneous, hypechoic lesions compared to the thyroid on the ultrasonography examination. They can be detected easily when they are more than 1 cm. However, cystic parathyroid adenomas are rare. When present, they appear as decreased echogenic areas in the gland. Extrathyroidal feeding from an artery at one pole of the gland is characteristic which is seen on Doppler imaging. We aimed to present a case series including seven cases in which glands looked partially cystic and heterogeneous from the 88 primary hyperparathyroidism patients presented to our clinic.

### Materials and methods

Eighty-eight patients who were diagnosed with primary hyperparathyroidism between January 2010 and September 2012 were reviewed retrospectively. All the cases were diagnosed with primary hyperparathyroidism in the endocrinology outpatient clinic for room surgery was planned. All the cases were confirmed to have primary hyperparathyroidism histologically. Sonographic images and reports were obtained from the archives and they were reanalyzed. All of the ultrasonography images were taken by high resolution superficial tissue probes with 13 MHz (Hitachi EUB 7000, Tokyo, Japan). The inside of the lesions looked frequently highly hypechoic and homogeneous but less hypechoic compared to solid and strap muscles. Six cases which had atypical appearance with a lesion that was heterogeneous and included cystic areas were separated and investigated further. Demographic features of those patients were as follows: mean age was 51 ± 14.5 and all of them were female. All of these cases were sent to ultrasonography because of suspicion of a parathyroid lesion based on clinical and laboratory evidence including elevated parathyroid hormone and or high serum calcium values. On the ultrasound, five of the lesions were located on the left and one was located on the right and they were frequently observed postero-inferior to the thyroid lobe on the left. Sonographically, the longitudinal dimention of the adenomas were more than 2 cm (by dimention: 2.8 ± 0.7). Mean PTH: 183 ± 58; Ca = 10.9 ± 0.8. Both mean PTH and calcium were elevated. In histopathologic examination all cases were diagnosed with parathyroid adenoma.

### Conclusion

Cystic parathyroid adenomas are presented in the literature as case reports. Cystic parathyroid adenomas were more frequently detected in our clinic then reported in the literature (7%), and clinically our cases had higher PTH and calcium values and a larger dimensions compared to the cases reported in the literature. Based on these features our patients may need to be evaluated as a separate group.

DOI: 10.1530/endoabs.32.P143

## Primary hypoparathyroidism and autoimmune endocrine disorders

### Ana Martins1, João Martin Martini1,2, Sónia Vale1,2, Ana Gomes1, Gabriel Miltenberger-Miltenyi1,2 & Isabel Cañro1,2

1Santa María’s Hospital, Lisbon, Portugal; 2Lisbon Medical School, Lisbon, Portugal.

### Introduction

Primary hypoparathyroidism (PH) is a rare condition. After surgery and chronic alcoholism, an autoimmune disease is the most common etiology and must specifically be considered in the context of a patient with other autoimmune endocrine diseases.

### Case report

MASD a male caucasian patient aged 31, was admitted to the emergency department because of perioral and hand paresthesias, and carpal spasm, in the context of a generalized anxiety reaction. A previous diagnosis of Hashimoto’s thyroiditis treated with levothyroxine was reported. There were no other known diseases nor previous surgeries, alcohol consumption or drug use. Family history was unremarkable as it was physical examination, except for positive Chvostek and Trousseau signs. Analytical evaluation revealed hypocalcaemia with increased serum phosphate and normal albumin and arterial pH; hypercalciciuria was found. Serum PTH was low with normal 25-hydroxyvitaminD levels and normal parameters of bone formation and reabsorption as well as normal bone densitometry. Thyroid function was normal under therapy. Normal adrenal and pituitary function were found. Antibodies against parathyroid cells were negative. Genetic testing revealed the c.2066A > G(Gp.Arg990Gy) polymorphism at exon 6 of the calcium sensing receptor (CASR) gene.

### Discussion

PH is a very rare condition. In this patient, the presence of known Hashimoto’s thyroiditis made autoimmune PH the most likely diagnosis, suggesting a polyglandular autoimmune disease. However parathyroid auto-antibodies were negative and a specific polymorphism of the CASR gene was found that according to published data may be associated with gain of function of calcium sensor. Reported prevalence of this polymorphism is so low, that it must be considered causative in this patient. In conclusion in this young patient with autoimmune thyroid disease, PH was found in relation to a specific polymorphism of the CASR gene. A rose is not always a rose.

DOI: 10.1530/endoabs.32.P144
Primary hyperparathyroidism in people under 30

P145

Experience in the treatment of primary hyperparathyroidism with cinacalcet: data after 12 months of treatment

Ines Luque-Fernández1, Antonia Garcia-Martín2, Alessandra Luque-Pazos1, Julià Sastre-Marcos1, Almudena Vicente-Delgado3, Amparo Marco-Martínez3 & Bárbara Canaves4

1Virgen de la Salud Hospital, Toledo, Spain; 2Hospital Comarcal del noroeste, Caravaca de la Cruz, Spain.

Introduction

Cinacalcet is an oral calcimimetic indicated in treatment of primary hyperparathyroidism if patients do not accept surgery, do not carry out the surgical criteria, there is failure of previous surgery or serious comorbidity that makes surgery impossible.

Methods

Descriptive study that included 20 patients with primary hyperparathyroidism who had completed at least 12 months of treatment with cinacalcet for different reasons (eight patients refusal to parathyroidectomy, three surgery not possible due to comorbidities and nine progressive hypercalcemia prior to surgery). We recorded clinical and biochemical data at baseline, and after 3, 6, and 12 months of treatment.

Results

After 3 months of therapy, serum calcium was significantly decrease (10.7 vs 11.73 mg/dl, P<0.001) and serum phosphorus was significantly increased (2.62 vs 2.41 mg/dl, P=0.004) while no significant change occurred in serum PTH (181.91 vs 195.47, P=0.695). No further variation was observed after 6 months as compared to 3 months follow up. After 12 months serum PTH was significantly decreased as compared to baseline (152.47 vs 181.91, P=0.028) as well as serum calcium (10.2 vs 11.73 mg/dl, P<0.001) and phosphorus levels (2.71 vs 2.41 mg/dl, P=0.01). Normocalcemia (S-Ca <10.1 mg/dl) was achieved in 55% of patients.

Usually the medication was well-tolerated. Most common adverse events were nausea and vomiting, especially at the beginning of therapy.

Conclusion

Hypercalcemia is rapidly improved by cinacalcet and remains stable after 12 months follow-up. Cinacalcet is an effective alternative in non-surgical treatment of primary hyperparathyroidism in patients with recurrent disease or in case of surgical contraindications. Furthermore, cinacalcet may be useful in the preoperative hypercalcemia management.

DOI: 10.1530/endoabs.32.P145

Primary hyperparathyroidism in people under 30

P146

Fedala Saida & Chentli Farida

Department of Endocrine and Metabolic Diseases, Bab El Oued Hospital, Algiers, Algeria.

Introduction

Primary hyperparathyroidism (HPT) is usually observed in old people. It is very rare in children and young adults. Our aim is to analyze clinical, biological aspects, and outcome in six subjects under 30.

Methods

The six subjects were chosen among 36 people hospitalized for primary HPT from 2009 to 2012. All had clinical examination, routine analyses, biological (blood and urinary calcium and phosphorus, and vitamin D) and hormonal (at least three PTH) assessments. Radiological exploration was based on cervical ultrasound and MIBI scintigraphy. After medical treatment of severe hyper calcemia, they were all operated on, and followed.

Results

Mean age = 24 (18–30). Primary HPT seemed to be sporadic. Our patients suffered mainly from bone disorders (five cases) and from symptoms of severe hyper calcemia (n=1). Mean calcemia = 131.5 mg/l (85–110 mg/l); mean phosphorus = 23.8 mg/l (25–45 mg/l), mean PTH = 753.5 pg/ml (16–87 pg/ml). Calcemia was ≥ 140 mg/l in two. Ultrasound and MIBI showed a single parathyroid tumour in all of them. Histological study demonstrated five adenomas and one carcinoma. The tumour size was 2 cm in all cases. Research for MEN was negative. Genetic study could not be done for socio-economical problems. Five did not relapse for 1–7 years; however one was lost in sight.

Conclusion

Primary HPT is rare in people under 30. It is more symptomatic and more severe than in elderly, but the outcome seems better even for the case classified as malignant by histology as there is not any relapsing or metastasises for more than 7 years. In this study the single parathyroid lesion seemed to be sporadic as we

P147

An extensive precipitation of calcium in subcutaneous tissue in patient with juvenile dermatomyositis

Olivera Boskovic, Sanja Borozan, Snezana Vujosevic, Sreten Kavaric, Aleksandar Djogo, Koviljka Kazic & Sanja Medenica

Clinical Center of Montenegro, Podgorica, Montenegro, Montenegro.

Introduction

Juvenile dermatomyositis may be associated with advanced calcinosis but the mechanisms that leads to their development remains unclear.

Case report

A female patient admitted to the hospital at the age of 17 for skin rash, malaise and pain in peripheral joints and muscles. Congenital bilateral hip dysplasia. After evaluation a syndrome overlap with dominant atypical dermatomyositis and SLE was suspected and treatment with prednisolone and choquorine initiated. Six months after, subcutaneous calcium deposits appeared, first in gluteal region, than polytopically. No metabolic disorders were observed; levels of PTH, phosphorus and calcium have always been in reference range, ANA and anti-dsDNA occasionally elevated.

During the last 12 years, different immunosuppressive treatments: methotrexate, cyclophosphamide, azathioprin, myko phosphol, colchicine, intravenous bisfosfo nates, immunsoglobin and calcium antagonists were given in attempt to stop spreading and reduce a calcinosis but without any improvement.

Presently, patient has a Gottron papules on MCP and PIP joints of both hands. A very prominent extensive subcutaneous calcinosis with a few skin ulcers (from which calcium is leaking) is over thorax, abdomen, proximal part of both hands, legs and pelvis, emphasized in lateral part of a right hip. The hands, distal parts of both legs and feet are spared. The muscles are atrophic and thin. Third muscle biopsy showed no calcifications but an increased number of macrophages in the perimysium, a few CD3 T-cells in the endomysial areas.

According to the early onset and a widespread calcinosis, a diagnosis of juvenile dermatomyositis is established. Last year, Hashimoto thyroiditis and interstitial lung disease are diagnosed.

Sedimentation rate remains elevated which, with a current health condition, despite the prolonged treatment, indicates that disease is in active phase. Lastly, a treatment with abatacept (alternatively rituximab) was recommended.

Conclusion

Revealing a pathogenesis of calcium deposits would certainly bring a new insight to the patient.

DOI: 10.1530/endoabs.32.P147

Measurement of 25-hydroxyvitamin D: evaluation of the new DIAsource ELISA assay

Sophie Huvelle1, Thibault Lepoutre1, Nicolas Heureux2 & Damien Gruson1

1Department of Clinical Chemistry, Cliniques Universitaires St-Luc and Université Catholique de Louvain, Brussels, Belgium; 2DiaSource, Brussels, Belgium.

Background

Vitamin D is an important contributor to musculoskeletal health and its potential involvement has recently been underlined in several non-skeletal diseases. Measurement of circulating levels of 25-hydroxyvitamin D (25OHD) represents the most reliable assessment of vitamin D status. Several assays are available but are not commutable because of a lack of of standardization. The aim of our study was to evaluate the performance of a new ELISA for measurement of 25OHD levels.

Methods

25OHD levels were measured with a newly released ELISA (DIAsource Immunoassays), a simplified method without pre-treatment step. Method comparison was performed using 199 patients’ samples with automated chemiluminescent immunoassay commonly used in clinical laboratories (Liaison, DiaSorin).

Results

According to our automated assay routine cut-points, serum concentrations of 25OHD were below 20 ng/ml in 96 patients, between 20 and 30 ng/ml in 68 patients and above 30 ng/ml in 35. The ELISA and the automated methods

Endocrine Abstracts (2013) Vol 32
Objective
To assess the prevalence of multiple endocrine neoplasia type 1 (MEN1) in patients with symptomatic primary hyperparathyroidism (PHPT).

Methods
A retrospective analysis of 75 consecutive patients with symptomatic PHPT from January 1994 to July 2012 was done, who underwent parathyroid surgery at our centre. Five patients had MEN1 syndrome. Among them 1 was familial MEN1. The patients with MEN1 were analyzed based on clinical presentation, biochemical and hormonal profile, imaging modalities and treatment outcome.

Results
Mean age of the study patients was 28.6 ± 12.9 years (male:female = 4:1). Mean age of the rest all patients was 43.5 ± 11.5 years. Four were symptomatic at presentation and one was diagnosed on family screening. Mean duration of symptoms was 23.8 ± 12.1 months. Bone pains and painful proximal myopathy were the commonest presentation (4/4), followed by pathological fractures in one case. Distal renal tubular acidosis was diagnosed in one case, which normalized after surgery. The most common presenting manifestation was PHPT in four patients (80%), followed by hyperparathyroidism due to pituitary tumor in one patient (20%). PHPT was a universal feature (100%) in all MEN1 syndrome followed by pituitary tumors in three cases (60%) and enteropancreatic neuroendocrine tumors in two cases (40%), with both being insulinoma. Among the pituitary tumors, prolactinoma and nonfunctioning pituitary adenoma were present in two in each case demonstrating equal prevalence.

All PHPT patients underwent parathyroidecomy and the ones with MEN1 had mean parathyroid gland weight was 835.4 ± 178.5 mg, which was larger than the rest (mean parathyroid gland weight was 1355.6 ± 684.5 mg, which was larger than the rest (K = 3.4546 to K = 0.3363). A small negative difference (2.7905 ng/ml; 95% CI = 3.4546 to –2.1265) was highlighted, for the ELISA method through the Bland and Altman plot and important discrepancies (higher than 10 ng/ml) were observed in 12 samples.

Conclusions
Our preliminary results showed that the new 25OHD ELISA assay demonstrated a good agreement with a commonly used assay. A small difference was evidenced but its clinical impact is limited. However, additional investigations will be required to confirm the performances of this new simplified ELISA assay.

DOI: 10.1530/endoabs.32.P150

P149 Persistent primary hyperparathyroidism
Irina Kotova, Alexander Gaidyra, Dmitry Alayev & Elena Martino
M.F. Vladimirsky Moscow Regional Clinical and Research Institute, Moscow, Russia.

Introduction
Achievement of stable normocalcemia (88–98.8%) is considered a criterium of efficiency of surgical operations for primary hyperparathyroidism (PHPT) (P. Gouret al. 2001, Zeiger 1997). In 1–15% of cases, persistence of PHPT is noted (Mariani et al. 2003, Mariette et al. 1998).

Description of methods
In 110 of 175 patients (aged 14–72 years), parathyroid adenoma was verified, in 57 – hyperplasia, and in 8 – parathyroid cancer. All patients underwent determination of total and ionized calcium levels, blood parathyroid hormone (PTH) levels, ultrasound imaging, PTG scintigraphy with 99mTc-sestamibi and single photon emission computed tomography (SPECT) as well as roentgen computed tomography.

Results
In seven patients, persistent PHPT was revealed due to insufficient operation volume in parathyroid hyperplasia. During first operation, one pathological gland was removed in four patients, two glands – in two, and three – in one patient. Temporary positive effect was noticed in all patients (decrease of PTH and calcium levels). In two patients, hyperplastic glands missed during first operation were located in anterior mediastinum. In one patient, three pathological glands were removed and repeated operation included sternotomy and removal of one additional hyperplastic ectopic gland from thymus. In other (female) patient, two hyperplastic parathyroid glands were removed during first operation and during repeated operation – one additional ectopic gland from the thymic peduncle. In two patients, repeated operations were associated with unrevealed parathyroid ectopia into the paraesophageal space. In the other female patient, only one parathyroid gland was removed during first operation; the other neoplasms removed as PTG turned out lymphatic nodes. During repeated operation, three hyperplastic parathyroid glands were removed. Two female patients are followed up in ambulatory. In one of them, in addition to one hyperplastic parathyroid gland, two neoplasms taken first for PTG were removed but then were verified histologically as lymphatic nodes. In the second of them, two parathyroid adenomas were removed but histologically they turned out hyperplastic PTG. Now both patients are under additional examination.

Conclusion
PHPT persistence is caused by inadequate operation volume in cases of PTG hyperplasia. The special difficulty of intraoperative differential diagnostics of morphological PHPT forms is due to the fact that, in cases of hyperplasia, parathyroid glands become hypoplastic asynchronously, and in cases of hyperplasia, they become hyperplastic also non-simultaneously. Biopsy of visually non-elongated PTG is necessary. Observation of double parathyroid adenomas is either mistaken or they are casuistically rare.

DOI: 10.1530/endoabs.32.P150

P151 Does the severity of vitamin D deficiency affect the prevalence of gastrointestinal polyps?
Ozlem Yonem1, Hilini Ataseven1, Sebila Dokmetas2, Hatice Ozer3 & Fatih Kilic3
1Department of Gastroenterology, Cukurcayir University, Sivas, Turkey; 2Department of Endocrinology, Cukurcayir University, Sivas, Turkey; 3Department of Pathology, Cukurcayir University, Sivas, Turkey.

Introduction
The beneficial effects of vitamin D against gastrointestinal polyps and cancer in the gastrointestinal system as a whole remain unknown and relevance in repeat populations remain controversial. Also in most studies the role of accompanying hypocalcemia itself is often neglected. For this reason we included only patients with low vitamin D levels and investigated the presence of gastric and colonic polyps.

Methods/design
Between March 2011 and September 2012, we investigated 25(OH) vitamin D levels in patients with clinical suspicion. We then performed colonoscopy and/or endoscopy in patients having clinical indications for these procedures.

Results
A total of 301 patients (175 female, 126 male) were divided into three groups according to their serum 25(OH) vitamin D levels: group 1: 0–10, group 2: 10–20, group 3: 20–30. 246 patients underwent colonoscopy and endoscopy while 55 cases underwent only colonoscopy. There was a total of five cancer cases (two colon, three gastric cancer) and four of these cases belonged to group 1 and one patient to group 2. We found colonic polyps in 29, 44, and 8 cases in groups 1, 2, and 3 respectively. The difference between the groups 1, 2, and 3 by means of poly presence was significant. We found polyps by upper endoscopy in only 12 cases. We found a significant correlation between colonic polyps and increased

DOI: 10.1530/endoabs.32.P150

P150 Prevalence of multiple endocrine neoplasia type 1 syndrome in primary hyperparathyroidism
Sunil Kumar Kota1, Lalit Kumar Meher2, Sriti Jammula3 & Kirtikumar D Modi4
1Medwin Hospital, Hyderabad, Andhrapradesh, India; 2MKCG Medical College, Berhampur, Orissa, India; 3Rohan Institute of Pharmaceutical Sciences, Berhampur, Orissa, India.

Objective
To assess the prevalence of multiple endocrine neoplasia type 1 (MEN1) in patients with symptomatic primary hyperparathyroidism (PHPT).

Methods
A retrospective analysis of 75 consecutive patients with symptomatic PHPT from January 1994 to July 2012 was done, who underwent parathyroid surgery at our centre. Five patients had MEN1 syndrome. Among them 1 was familial MEN1. The patients with MEN1 were analyzed based on clinical presentation, biochemical and hormonal profile, imaging modalities and treatment outcome.

Results
Mean age of the study patients was 28.6 ± 12.9 years (male:female = 4:1). Mean age of the rest all patients was 43.5 ± 11.5 years. Four were symptomatic at presentation and one was diagnosed on family screening. Mean duration of symptoms was 23.8 ± 12.1 months. Bone pains and painful proximal myopathy were the commonest presentation (4/4), followed by pathological fractures in one case. Distal renal tubular acidosis was diagnosed in one case, which normalized after surgery. The most common presenting manifestation was PHPT in four patients (80%), followed by hyperparathyroidism due to pituitary tumor in one patient (20%). PHPT was a universal feature (100%) in all MEN1 syndrome followed by pituitary tumors in three cases (60%) and enteropancreatic neuroendocrine tumors in two cases (40%), with both being insulinoma. Among the pituitary tumors, prolactinoma and nonfunctioning pituitary adenoma were present in two in each case demonstrating equal prevalence.

All PHPT patients underwent parathyroidecomy and the ones with MEN1 had mean parathyroid gland weight was 835.4 ± 178.5 mg, which was larger than the rest (mean parathyroid gland weight was 1355.6 ± 684.5 mg, which was larger than the rest (K = 3.4546 to K = 0.3363). A small negative difference (2.7905 ng/ml; 95% CI = 3.4546 to –2.1265) was highlighted, for the ELISA method through the Bland and Altman plot and important discrepancies (higher than 10 ng/ml) were observed in 12 samples.

Conclusions
Our preliminary results showed that the new 25OHD ELISA assay demonstrated a good agreement with a commonly used assay. A small difference was evidenced but its clinical impact is limited. However, additional investigations will be required to confirm the performances of this new simplified ELISA assay.

DOI: 10.1530/endoabs.32.P150

Endocrine Abstracts (2013) Vol 32
age, high Bun and creatinine levels and increased visceral fat but not with BMI, body fat percent, H.pylori presence, SES or SCS. But both endoscopic and colonoscopic polyp presence was found to be significantly increased in diabetic patients.

Conclusion
The severity of vitamin D deficiency is important for both stomach and colon cancers. We emphasize the importance of diabetes mellitus and visceral fat in the prevalence of endoscopic and colonic polyps. Further studies with larger number of patients are needed to confirm our results.

DOI: 10.1530/endoabs.32.P151

---

### P152

**Vitamin D deficit and metabolic syndrome**

Inmaculada González-Molero, Gemma Rojo, Marta Domínguez-López, Eleazarra Rubio, Carolina Gutierrez, Sonsoles Morcillo, Isabel Esteva, Marisol Ruiz de Adana & Federico Soriguer

Endocrinology Service, Carlos Haya Hospital, Málaga, Spain.

**Background and aims**
To assess the relationship between 25-hydroxyvitamin D levels and prevalence and incidence of metabolic syndrome.

**Methods**
We undertook a population-based cohort study in Spain. At baseline (1996–1998), 1226 subjects were evaluated. Follow-up visits were performed in 2002–2004 and 2005–2007. At baseline and follow-up, participants underwent an interview and a standardized clinical examination with an oral glucose tolerance test in those subjects without known diabetes. At the second visit, 25-hydroxyvitamin D levels and iPTH levels were measured.

**Results**
The prevalence of metabolic syndrome (IDF criteria) at the second and third visit was 29.4 and 42.5% respectively. Mean levels of 25-hydroxyvitamin D were lower in subjects with metabolic syndrome: 21.7 ± 6.21 vs 23.35 ± 6.29 ng/ml, P = 0.001. The prevalence of vitamin D deficiency (25-hydroxyvitamin D ≤ 20 ng/ml) at the second evaluation was 34.7%, with significant differences between subjects with and without metabolic syndrome (34.6 vs 26.5%, P = 0.01). Men with vitamin D deficiency more frequently had hypertension and metabolic syndrome than men with normal levels. Women with vitamin D deficiency had more frequently hyperglycemia, hypertension, increased waist circumference and hypertriglyceridemia. The number of present criteria was related to the prevalence of vitamin D deficiency so that for 1, 2, 3, 4, and 5 criteria the prevalence were: 31.7, 32, 33.5, 55.4, and 100%. In prospective study, 25-hydroxyvitamin D values ≤ 20 ng/ml were not significantly associated with an increased risk of developing metabolic syndrome in the next 4 years (OR = 0.99, 95% CI 0.57–1.7, P = 0.97) after adjusting by sex and age.

**Conclusions**
Vitamin D deficiency is associated with an increased prevalence but not with increased incidence of metabolic syndrome.

DOI: 10.1530/endoabs.32.P152

---

### P154

**Vitamin D deficiency in morbid obesity before and after bariatric surgery**

Inmaculada González-Molero, Montserrat Gonzalo-Marín, Marta Domínguez & Juan García Arráez

Endocrinology Service, Carlos Haya Hospital, Málaga, Spain.

**Rationale**
Patients with morbid obesity may have vitamin D deficiency and bariatric surgery may exacerbate it due to various factors such as lack of dietary compliance, reduced intake, malabsorption, etc.

**Objective**
To study the prevalence of vitamin D deficiency in patients with morbid obesity before and after bariatric surgery and its relationship with other laboratory parameters.

**Methods**
A retrospective study of 72 morbidly obese patients before and 1 year after surgery (bypass or sleeve). We collected data about: age, sex, previous comorbidities, physical examination, impedance testing, and laboratory parameters (25-hydroxyvit D, iPTH, Ca, HbA1c, total cholesterol, LDL, HDL, triglycerides, uric acid, and leptin).

**Results**
The mean age of patients was 45.84 ± 10.39 years, 78.4% women. Pre- and postoperatively, BMI 51.51 ± 8.11 and 33.62 ± 5.21 (P < 0.001). One year after surgery there were significant decreases in HbA1c, TC, LDL, triglycerides, uric acid, leptin, and HDL level. Mean serum 25-OH vit D pre and post were: 16.96 ± 7.87 vs 22.53 ± 12.44 (P < 0.013) and iPTH: 16.9 ± 43.97 vs 41.79 ± 2.1, 89 (NS). The percentage of vitamin D deficiency (≤ 20 ng/ml) were pre and post: 71.8 vs 44.9% (P = 0.04) and hyperparathyroidism 19.4 vs 14.6% (NS). Vitamin D levels negatively correlated with preoperative age, body fat percentage and iPTH. Vitamin D levels negatively correlated with postoperative BMI, leptin, total cholesterol, and HbA1c.

**Conclusions**
Patients with morbid obesity have vitamin D deficiency in 71.8% of cases preoperatively, which should lead us to measure 25OH vitamin D levels routinely in patients with morbid obesity. After the surgical procedure, despite supplementation with vitamin D, patients maintain a high percentage of vitamin D deficiency (44.9%) and elevated iPTH.

DOI: 10.1530/endoabs.32.P154

---

### P155

**The association of low serum 25-hydroxyvitamin D and serum osteocalcin levels with the metabolic syndrome in females with polycystic ovary syndrome in Al-Baha region, Saudia Arabia: a case–control study**

Ghada el Sagheer, Latifa Guddah & Ahmad Saad Al Deen

King Fahad Hospital, Al Baha, Saudi Arabia.

**Background**
Polycystic ovary syndrome (PCOS) is a common endocrine disorder in females of reproductive age. It is frequently associated with metabolic disturbances and insulin resistance, that occurs in about 50–70%. Evidences were reported about the association between vitamin D and osteocalcin with cardiovascular risk factors, regulation of insulin secretion and sensitivity.

**Objectives**
Evaluation of the association between low 25-hydroxyvitamin D (25(OH) D) and serum osteocalcin levels and the components of metabolic syndrome (MS) in women with PCOS in Al-Baha region, Kingdom of Saudi Arabia (KSA)

**Methods**
Sixty patients with PCOS were chosen from the attendants of the Endocrinology out-patient clinic in KFH at Al-Baha, KSA. Standard metabolic, endocrine, and
anthropometric measurements were evaluated for all patients, including 25(OH)D and osteocalcin levels and oral glucose tolerance tests.

Results

The prevalence of 25(OH)D deficiency (<30 ng/ml) was 60%. Seventeen patients (28%) showed association between MS and PCOS. Patients with MS had significantly lower level of serum 25(OH)D, osteocalcin, and CRP (P<0.0001). Patients with low serum 25(OH)D had significantly higher age, weight, BMI, waist and hip circumference (WHR), and systolic blood pressure (SBP); 1-h glucose, homeostatic model assessment-insulin resistance (HOMA-IR), fasting insulin, triglycerides, and CRP. They had significantly lower levels of HOMA-B; quantitative insulin sensitivity check index (QUICKI), and HDL cholesterol (P<0.00 for all). Osteocalcin levels had significantly negative correlation with SBP and diastolic blood pressure (DBP), CRP, BMI, fasting and 1-h glucose, triglycerides and HOMA-IR (P<0.00, 0.01, 0.003, 0.000, 0.000, 0.000, 0.00, and 0.00 respectively). It has significant positive correlation with QUICKI, and HDL. In multivariate regression analysis, 25(OH)D was an independent predictors of HOMA-IR and QUICKI (P<0.05). Fasting insulin, SBP, and HDL were significant and independent predictors of osteocalcin.

Conclusions

Low levels of 25(OH)D and osteocalcin were associated with the features of MS in PCOS women. Large intervention trials are warranted to evaluate the effect of vitamin D supplementation in these cases.

Key words

25(OH)D, osteocalcin, MS, PCOS.

DOI: 10.1530/endoabs.32.P155

P156

MSIA–SRM assay for parathyroid hormone and vitamin D binding protein: correlation with clinical immunoassays methods and application to clinical samples

Caje Moniz1, Lewis Couchman1, Bryan Krastins1,2, Mary Lopez1,2, Amol Prakash1,2, David Sarracino1,2, Mary Vogelsang1,2, Scott Peterman1,2, Goumi Vadalà1,2, Sarah Robinson1

1Kings College Hospital, London, UK; 2BRIMS Centre, Boston, Massachusetts, USA.

Parathyroid hormone is involved in calcium homeostasis through interactions with vitamin D. Because intact and truncated forms of PTH vary in their biological activity, assays that can accurately quantify the ratio of intact hormone to its fragments are of increasing significance in the diagnosis of endocrine, renal and bone diseases. Vitamin D and its metabolites circulate tightly bound to vitamin D-binding protein (DBP). Because DBP concentrations are altered in pregnancy, liver and renal diseases and also show genetic variations in different ethnic groups, total vitamin D in serum can be misleading. In addition, both calcium and vitamin D metabolites can decrease the secretion of parathyroid hormone (PTH).

Previously, we developed multiplexed mass spectrometric immunoassay (MSIA)–SRM assays for PTH that allow quantification of four fully-tryptic monitoring peptides (that span the entire PTH sequence) and two semi-trytic variant specific peptides (1). Using this approach, it is possible to monitor intact PTH and also the degree of N-terminal fragmentation.

In this study, the objective was to develop a multiplexed, MSIA–SRM-based targeted assay for PTH and DBP. We applied this MSIA–SRM assay and a commercially available immunoassay to a cohort of 500 clinical samples from a variety of different patient groups including renal disease, cancer, vitamin D deficiency and other conditions that can affect calcium homeostasis. The results demonstrated excellent assay linearity (R² = 0.90–0.99) with sensitivity for analytes in the published clinical ranges and limits of detection in the pg/ml range. Comparison of the PTH MSIA–SRM assay with the commercial ELISA assay demonstrated good correlation in normal subjects but important differences in renal failure. There were also some unusual fragments seen in clinical samples, not previously reported in the literature.

References


DOI: 10.1530/endoabs.32.P156

P157

Vitamin D deficiency, secondary hyperparathyroidism and its influence on bone mineral density

Vladyslav Povoroznyuk & Nataliya Balataska

Institute of Gerontology, NAMS of Ukraine, Kyiv, Ukraine.

Introduction

The consequences of vitamin D deficiency are secondary hyperparathyroidism and bone loss, leading to osteoporosis and fractures, mineralization defects, which may lead to osteomalacia in the long term, and muscle weakness, causing falls and fractures.

Objectives

The aim of the research was to determine the frequency of vitamin D deficiency, secondary hyperparathyroidism and it’s influence on bone mineral density in people of different ages.

Methods

There were examined 683 patients aged 20–94 years. 25(OH)D and iPTH level was evaluated by electrochemiluminescence method (Elecsys 2010, Roche). Vitamin D deficiency was defined as a 25(OH)D below 20 ng/ml (50 nmol/l), and vitamin D insufficiency as a 25(OH)D of 21–29 ng/ml (52.5–72.5 nmol/l). Bone mineral density (BMD) was studied by X-ray densitometry ‘Prodigy’.

Results

Only 6.1% of people had normal level of vitamin D, vitamin D deficiency was recorded in 81.4% patients. In 16.8% the amount of 25(OH)D was below the minimal level that can machine determine. Significantly higher level of 25(OH)D recorded in summer months, and the lowest – in the winter-spring season. Secondary hyperparathyroidism diagnosed in 11.6% patients. It was found the negative correlation between the levels of 25(OH)D and parathyroid hormone (r = −0.16, P = 0.0001). It was shown that only people with vitamin D deficiency have significant negative correlations between the level of parathyroid hormone and BMD at the neck and proximal femur (r = −0.14, P = 0.005 and r = −0.13, P = 0.04 respectively), upper and lower extremities (r = −0.11, P = 0.02) and UD forearm (r = −0.11, P = 0.03).

Conclusion

Deficiency of vitamin D leads the increasing of the level of parathyroid hormone, which decreasing BMD, mainly in areas of the skeleton composed of compact bone tissue.

DOI: 10.1530/endoabs.32.P157

P158

Comparative study of bone metabolic parameters and vitamin D levels of fertile aged women, suffering from different bone metabolism altering diseases

Orsolya Acs1, Bence T Acs1,2, Csaba Horvath3, Viktoria Ferencz3, Szilvia Meszaros3, Edit Toth4 & Emoke Csupor5

1Semmelweis University School of Ph.D. Studies, Budapest, Hungary; 22nd Department of Internal Medicine, Semmelweis University, Budapest, Hungary; 31st Department of Internal Medicine, Semmelweis University, Budapest, Hungary; 4Department of Rheumatology, County Hospital Flor Ferenc, Budapest, Hungary; 5The Health Service of Budavari Local Authorities, Endocrinology, Budapest, Hungary.

Introduction

Polyzystic ovary syndrome (PCOS), lactase deficiency, nephrolithiasis and thyroid diseases are considered endemic. The aim of our study was to evaluate which of the above-mentioned diseases affect the most the bone metabolic parameters, bone mineral density (BMD) and the prevalence of bone fractures in fertile aged women.

Materials and methods

A total of 92 fertile aged women (32.6±2.5 years) were divided into four groups (23 in each) according to their diseases (PCOS or lactase deficiency or nephrolithiasis or treated hypothyroidism). BMD was measured by dual-energy X-ray absorptiometry (DEXA). Laboratory analysis included routine and also calcium metabolism: 25-hydroxyvitamin D (25-(OH)D), parathyroid hormone (PTH), β-CrossLaps, 25-OH D3, vitamin D, osteocalcin (OC). The prevalence of bone fractures were also recorded. Statistical analysis was performed by ANOVA, with post-hoc Bonferroni’s correction (Statistica Software 9.0).
Results
After comparing the results of the groups, women with nephrolithiasis had the lowest BMD (Zsc: −0.92±0.35) (P<0.05) in the region of lumbar spines (L2–4), the lowest BMD (Zsc: −1.33±0.43) (P<0.05) in the region of the femoral neck, and lowest BMD (Zsc: −1.19±0.31) (P<0.05) at the one third of distal radius among all groups. The average bone fracture rate of the 92 fertile aged women was high (40.8%), and serum 25-(OH) vitamin D3 levels were low (27.8±6.1-364.± 6.4 nmol/l) comparing to the normal range.

Conclusion
The recognition and treatment (for e.g. sufficient supplementation of vitamin D) of endemic diseases in women in fertile age should become part of the osteological and fracture prevention.

DOI: 10.1530/endoabs.32.P159

P159
Structure and frequency of clinical manifestations of primary hyperparathyroidism
Elena Brutskaya-Stempkovskaya1, Alla Shepelkevich2, Irina Bilodid3, Ekaterina Klausova4 & Veronika Lobshova4
1Thirty one Out-Patients Clinic of Minsk-City, Minsk, Belarus; 2Belarusian State Medical University, Minsk, Belarus; 3Minsk-City Endocrinology-center, Minsk, Belarus; 4Belarusian State Medical University, Minsk, Belarus; 5Belarusian State Medical University, Minsk, Belarus.

Introduction
Primary hyperparathyroidism (PHPT) is a result of overproduction of parathyroid hormone with pathologically changed parathyroid glands (PTG) and calcium-phosphorus metabolism disorders. Until now, PHPT is often detected late (in countries where there is no screening for hypercalcemia), when there are irreversible complications it manifested.

Materials and methods
One hundred and nine patients with PHPT (mean age: 52.2±8.7 years, duration disease: 8.6±4.3 years) were included in the retrospective study. The control group consisted of 55 age, gender matched subjects. Questionnaire survey (anamnesis data, risk factors for osteoporosis), parameters of calcium-phosphorus metabolism (PTH, Ca, Ca2+, P), bone markers (alkaline phosphatase, N-MID osteocalcin, PTHrP), sonography of the thyroid (PTG), scintigraphy PTG, bone mineral density (BMD) were examined.

Results
Among the examined patients the male-female ratio was 1:15 (7:102). Premenopausal women represented 28.4% (29) of the examined patients; postmenopausal women -71.6% (73). Mild PHPT was revealed in 23% patients, symptomatic PHPT – in 77%. Visceral form of disease was diagnosed in 21% patients, bone disorders – in 21% surveyed, mixed forms – in 35%. Low bone mineral density was detected in 75.9% (34.5%, osteoporosis; 41.4%, osteopenia) patients with PHPT; in the control group: 29.2 and 16.7% respectively. Clinical manifestations of symptomatic PHPT were: urolithiasis in 21% patients, cholelithiasis, 5.6%; a stomach ulcer and duodenal ulcer, 6.7%; fragility fractures had 11% of the examined patients.

Conclusion
The results of the retrospective study suggest the late diagnosis of PHPT, mostly the manifest forms associated with complications of PHPT and the low diagnostic rate of mild forms of PHPT, which necessitates the introduction of screening for hypercalcemia.

DOI: 10.1530/endoabs.32.P159

P160
A case report: hyperparathyroidism, nephrocalcinosis, and replacement therapy
Serife Nur Boysan, Zeren Ozgen & Tuna Sahin
Necip Fazil City Hospital, Kahramanmaras, Turkey.

Introduction
There is a risk of hypercalcemia, nephrolithiasis, nephrocalcinosis, and renal failure in the treatment of hyperparathyroidism. We present a case who has an improvement of this complication after changing large doses of vitamin D to physiological doses of 1,25(OH)2D itself.

Case report
A 50 years old man was admitted to hospital. He had idiopathic hypoparathyroidism from the age of 24. He was using oral 1,25(OH)2D 0.25 µg, 1333 IU Vit D, and 2500 mg calcium carbonate and also 880 IU Vit D/day. Physical examination was normal. Laboratory tests were revealed the serum creatinine as 1.3 mg/dl but serum calcium was 7.6 mg/dl and serum phosphorus was 5 mg/dl. Renal US confirmed mediulary nephrocalcinosis.

The therapy was changed to 1,25(OH)2D 0.25 µg 2x1/day and and 2500 mg calcium carbonate and also 880 IU Vit D/day. We followed serum calcium and phosphorus for monthly, serum creatinine for every 3 month and renal USG for every 6 month.

After 6 months of therapy, serum calcium was 8.8 mg/dl, serum phosphorus was 4.1 mg/dl, and serum creatinine was 1.3 but surprisingly renal US showed an important improvement in sonographic appearance of mediulary calcincosis.

Conclusion
Some literature suggests the use of injectable PTH(1–34) for this complication. However, PTH is not approved by FDA for use in hypoparathyroidism in USA because of the unknown risk of osteosarcoma. In Turkey we can only use as a drug except of indication with the permission of Health Ministry.

In this case; changing the therapy to physiological doses of 1,25(OH)2D and adding elemental calcium a dose for maintaining serum calcium level near the lower limit of normal reference values a degree of some improvement was provided.

DOI: 10.1530/endoabs.32.P160

P161
Abstract withdrawn.

DOI: 10.1530/endoabs.32.P161

P162
The prognostic value of peripheral neuropathy for the mortality and its relation to secondary hyperparathyroidism: a 10-month follow up of 97 patients with end-stage renal disease
Dragan Tesic1 & Nikola Curic2
1Clinic of Endocrinology, Diabetes and Metabolic Disorders, Novi Sad, Serbia; 2Department of Patophysiology, Novi Sad, Serbia.

Introduction and objectives
The aim of this study was to evaluate the risk of death in relation to hemodialysis. Material and methods
We performed a 10-month follow up study of hemodialysed patients attending our Center. A total of 97 patients were evaluated: 37 (38.1%) nephroangiosclerosis, 28 (28.9%) diabetic nephropathy, 18 (18.6%), and glomerulonephritis (14.4%) other causes. Somatic sensory neuropathy (PN) was documented using the Neuropathy Disability Score (NDS), vibration perception threshold (VPT) was measured by semi quantitative tuning fork C128 (grades 0–8) and AR (ankle jerk reflex) were recorded.

Results
Thirteen patients died (13.4%), 12 from the two first groups, none of the third group. Patients who died of other differed by: age (64.2±11.2 vs 55±12.9 years, P 0.02), CRP (13.7±10.5 vs 7.2±8.8 mg/l, P 0.03), BMI high (32.8±6 vs 29.3±5.9, P 0.06), AR (3.5±0.9 vs 2.3±1.8, P 0.02), NDS (5.8±7.3 vs 5.8±7.3, P 0.03), albumin level (34±5.1 vs 38±2.9 g/l, P 0.06), duration of dialysis (2.3±2.3 vs 5.2±4.9 years, P 0.04), and VPT (3.2±3.2 vs 5.1±2.5, P 0.001). There were no differences in parathropism (PTH) between groups (180.9±264 vs 318±498 pg/ml, P 0.42). Simple regression analysis of NDS of the whole 97 patients: HDL chol (r +0.23, P 0.04), Hb (r −0.20, P 0.05), BG (blood glucose; r +0.37, P 0.0003), PTH (r −0.21, P 0.047), creatinine (r −0.30, P 0.003), duration of dialysis (r −0.34, P 0.000), ABPI (ankle brachial pressure index, r +0.20, P 0.02). In multiple regression model as a significant deterioration of neuropathy (NDS) remains only: body height (P 0.005), blood glucose (P 0.08) and PTH (P 0.04).

Endocrine Abstracts (2013) Vol 32
Conclusions
This study showed that PN was a prognostic factor for death in dialysed patients and its failure was associated with elevated BG and lower PTH. So, the treatment of secondary hyperparathyroidism in hemodialysed patient is not indicated in at least those patient with developed peripheral neuropathy.

DOI: 10.1530/endoabs.32.P162

---

P163
Post-surgical hypoparathyroidism with ‘normal’ PTH
Teresa Azevedo, Teresa Martins, Manuel Lemos, Nuno Cunha, Frederico Valido & Fernando Rodrigues
IPO-Coimbra, Coimbra, Portugal.

Introduction
Hypoparathyroidism is characterized by hypocalcemia and low or inappropriately normal levels of PTH. It is the most common cause of hypoparathyroidism and is iatrogenic due to anterior neck surgery. In recent years it was documented that vitamin D insufficiency is widespread.

Aim
To investigate the cause of hypocalcemia in thyroidectomized patients with PTH within the reference range.

Methods
Retrospective review of clinical records of patients who underwent thyroid surgery with hypocalcemia and PTH within reference values. PTH was measured by chemiluminescent immunoassay (Immulus 2000) with reference values between 11 and 65 pg/ml and 25-OH-vitamin D was dosed by electrochemiluminescence (Cobas e411) with reference values between 30 and 100 ng/ml.

Results
We evaluated 16 patients (88% female) with a mean age (± s.d.) of 42 ± 14 years at the time of surgery. On postoperative evaluations, all of them had ‘normal’ PTH values with hypocalcemia, in which 11 needed calcium and/or calcitriol. Hypovitaminosis D was documented in 13 of 14 patients (93%) in which this parameter was assessed, of whom three had vitamin D < 10 ng/ml (deficiency) and ten had vitamin D between 10–30 ng/ml (insufficiency). In two patients vitamin D was not dosed. One patient had sufficient vitamin D (> 30 ng/ml).

Discussion/Conclusion
A normal PTH value does not exclude the presence of postsurgical hypoparathyroidism. Lack of vitamin D in patients with impaired parathyroid reserve may explain the hypocalcemia. These situations could probably benefit from treatment with calcitriol.

DOI: 10.1530/endoabs.32.P163

---

P164
Evaluation of concentration 25OH vitamin D3 selected patient population: preliminary report
Jystyna Nowak, Aneta Koszowska 1, Anna Bronczyk Puzon 1, Agata Kulpolk 2, Joanna Przybylska Just 1, Barbara Zabielewicz Szkodzinska 1,2 & Pawel Jagielski 3
1Department of Internal Medicine, Medical University of Silesia, Silesia, Poland; 2Department of Endocrinology, City Hospital in Piekar Slaskie, Silesia, Poland; 3Department of Genetic Diagnosis and Nutrigenomics, Medical College, Jagiellonian University, Malopolska, Poland.

Introduction
Vitamin D in the human body plays a very important role.

Aim
The aim of the study was to identify the differences in concentration of 25OH vitamin D3 in blood and compared with anthropometrics and biochemicals results of researched group of people.

Materials and methods
To research were included 212 patients hospitalized on Endocrinology Department of Hospital in Poland in 2012. Patients were divided into three groups adequately to the division created by Erik Erikson. As a correct values of 25OH vitamin D3 was adopted level above 30 ng/dl, as deficiency values 12–30 ng/dl, severe deficiency below <12 ng/dl. Obtained data were collected and analyzed in STATISTICA 10 program (statistical significance α = 0.05).

Results
The study included people aged 21–82 years. Among 74% of researched people were observed deficiency of 25OH vitamin D3, 15% of this group has severe deficiency. Significant statistical differences were observed between BMI in first and second group (P = 0.041); waist measurement value (WC) (P = 0.001), WHR value (P = 0.00002), the value of the WHR (P = 0.00021) in the first group and the second as well as the first and third.The differences were observed between concentration of total cholesterol level (P = 0.005), cholesterol LDL fraction (P = 0.015) and level of glycemic (P = 0.036) in first and second group.

Conclusions
Obtained results in research show that in age range 21–65 with age there is an increase of values: BMI, WHR, WHR, WC and increase concentration the level of total cholesterol, cholesterol LDL and glycemic levels.

DOI: 10.1530/endoabs.32.P164

---

P165
Evaluation of concentration 25OH vitamin D3 in the population over 65 years old: preliminary report
Anna Bronczyk Puzon 1, Justyna Nowak 1, Aneta Koszowska 1, Agata Kulpolk 2, Joanna Przybylska Just 1, Barbara Zabielewicz Szkodzinska 1,2 & Pawel Jagielski 3
1Department of Internal Medicine, Medical University of Silesia, Silesia, Poland; 2Department of Endocrinology, City Hospital in Piekar Slaskie, Silesia, Poland; 3Department of Geriatrics, City Hospital in Piekar Slaskie, Silesia, Poland; 4Department of Genetic Diagnosis and Nutrigenomics, Medical College, Jagiellonian University, Malopolska, Poland.

Introduction
Old age is defined as late adulthood and is an important part of human’s life. This is the time of life, when exist the real risk of 25OH vitamin D3 deficiency.

Aim
The aim of the study was find out the connections between concentration of 25OH vitamin D3 in blood and anthropometrics and biochemicals results depending on diseases in persons above 65 years.

Materials and methods
The research was conducted among patients hospitalized on Endocrinology Department of Hospital in Poland in 2012. Among research group chosen 50 persons which met the inclusion criteria: as age above 65 years. As a correct value of concentration of 25OH vitamin D3 in blood was adopted the level above 30 ng/dl, as deficiency level 12–30 ng/dl, for the severe deficiency value below 12 ng/dl. The results were collected and analyzed in STATISTICA 10 program (statistical significance α = 0.05).

Results
The research was conducted among persons in age 65–82 years. Mean concentrations (± s.d.) 25OH vitamin D3 was 20.8 ± 7.2 ng/dl. Among 80% of researched group was observed deficiency of concentration of 25OH vitamin D3, in this group 10% of researched persons had a severe deficiency Significant statistical differences were observed between concentration of 25OH vitamin D3 and waist circumference (P = 0.022). It was also a statistically significant correlation between serum 25OH vitamin D3 and WHR index (P = 0.018).

Conclusions
The results indicated that the lower concentrations of 25OH vitamin D3 were accompanied with higher value of index WHR and higher values of waist circumference.

DOI: 10.1530/endoabs.32.P165

---

Endocrine Abstracts (2013) Vol 32
P166
Cardio-metabolic risk factors in subjects with Vit D deficiency
Said Azzoug, Nassima Belhadj Aissa, Mourad Kesraoui, Lydia Lounis & Farida Chentli
Department of Endocrine and Metabolic Diseases, Bab Oued Hospital, Algiers, Algeria.

Introduction
Vitamin D (Vit D) is known for its action on bone metabolism. But recently more ubiquitous actions have been discovered. Vit D deficit is now considered as a world health problem because of it frequency and its consequences. Vit D deficiency seems to be involved in diabetes mellitus, and in autoimmune, neoplastic and cardio-metabolic diseases. The aim of our study was to analyze the incidence of cardio-metabolic diseases in a group of patients with vitamin D deficiency.

Subjects and methods
This retrospective study analyzed 23 patients with vitamin D deficiency (25OH vit D levels <30 ng/ml) diagnosed during the exploration of normocalcemic hyperparathyroidism.

Results
Mean age was equal to 57.5 ± 11 years. The mean BMI = 30.8 ± 7.21 kg/m². A BMI ≥ 25 kg/m² was found in 87% of our patients (56% were obese and 31% were overweight). Systemic high blood pressure was observed in 34.7%, 21.7% were dyslipidemic and 21.4% had glucose metabolism disorders.

Conclusion
In this study, although our subjects are relatively young, they are at high risk for cardio-metabolic diseases especially for obesity. But, as obesity interact on vitamin D deficiency; it is difficult to say which is the most deleterious for cardiovascular diseases. So, in future, prospective and large series with multivariate analyses are needed to confirm our results.

DOI: 10.1530/endoabs.32.P166

P167
Hyperparathyroidism: are male forms more or less aggressive?
Said Azzoug, Lydia Lounis, Nassima Beljdi Aissa, Mourad Kesraoui & Farida Chentli
Department of Endocrine and Metabolic Diseases, Bab Oued Hospital, Algiers, Algeria.

Introduction
Hyperparathyroidism (HPT) is a common disease prevailing in females (F). Male (M) forms are rare and their impact on the body is less studied than in females. Our aim is to see if male HPT is more or less aggressive than the female one. Subjects and methods
It is a retrospective study that took in account 62 HPT (46F, 16M) over a period of 7 years (2005–2012). All were questioned, examined, and had routine analyses, performed for comparison. The difference was considered as significant if P < 0.05.

Results
Mean age was equal to 57.5 ±11 years. The mean BMI = 30.8 ± 7.21 kg/m². A BMI ≥ 25 kg/m² was found in 87% of our patients (56% were obese and 31% were overweight). Systemic high blood pressure was observed in 34.7%, 21.7% were dyslipidemic and 21.4% had glucose metabolism disorders.

Conclusion
In this study where male HPT are less frequent than women’s, we observed that primary hyperparathyroidism was confirmed. The tests revealed a mild hypercalcemia with hypophosphatemia (2.5 mg/dl, normal 2.5–4.7 mg/dl) and hypercalciuria (408 mg/24 h normal values 100–300 mg/24 h). Although at advanced age and never been treated for osteoporosis, she had three pathological fractures and very low bone mineral density at all locations, radius included. These antecedents increased the supposition of supplementary metabolic disorder, other than postmenopause and/or senile status.

P168
A clinical case of complicated hyperparathyroidism with diagnosis delay due to vitamin D deficiency
Roxana Novac, Georgiana Constantinescu, Andreea Oprea, Voichita Mogos & Dumitru D Branisteau
St Spiridon Hospital, Iassy, Romania.

We present the case of a 75-year-old woman with a 10-year history of nephrolithiasis, for which she endured several sessions of extracorporeal shockwave lithotripsy (ESWL). She was directed to the Endocrinology unit for further investigations, due to persistent albeit minor increased values of blood calcium (10.48 mg/dl, normal 8.4–10.2 mg/dl). Here, the clinical supposition of primary hyperparathyroidism was confirmed. The tests revealed a mild hypercalcemia with hypophosphatemia (2.25 mg/dl, normal 2.5–4.7 mg/dl) and hypercalciuria (408 mg/24 h normal values 100–300 mg/24 h). Although at advanced age and never been treated for osteoporosis, she had three pathological fractures and very low bone mineral density at all locations, radius included. These antecedents increased the supposition of supplementary metabolic disorder, other than postmenopause and/or senile status.

Mean age was equal to 57.5 ± 11 years. The mean BMI = 30.8 ± 7.21 kg/m². A BMI ≥ 25 kg/m² was found in 87% of our patients (56% were obese and 31% were overweight). Systemic high blood pressure was observed in 34.7%, 21.7% were dyslipidemic and 21.4% had glucose metabolism disorders.

Our aim is to see if male HPT is more or less aggressive than the female one.

P169
Impact of vitamin D deficiency and oGH–IGF1 on cardiovascular risk in hypopituitary patients
Maria Cristina Savanelli, Elisabetta Scarano, Laura Vuolo, Vincenzo Brunelli, Manila Rubino, Annamaria Collao & Carolina Di Somma
Dipartimento di Medicina Clinica e Chirurgia Federico II University, Naples, Italy.

To determine a correlation between Vitamin D, GH, IGF1 and cardiovascular risk we enrolled 41 GHD patients (22 M, 19 F, age 18–84 years) and 41 controls. In all we determined: anthropometric parameters, blood pressure (BP), lipid and glucose profile, PTH, 25-OH-vitamin D, GH peak after GHRH + ARG, IGF1. Metabolic syndrome (MS) was evaluated by the IDF criteria. The vitamin D were lower in patients than in controls (21.3 ± 12.3 vs 28.2 ± 9.4, P = 0.006). A deficiency of vitamin D (< 20 ng/ml) was found in 51 vs 14.6% (P = 0.000), insufficiency (20–30 ng/ml) in 26.8 vs 41.4% (P = 0.27) and normal vitamin D (> 30 ng/ml) in 21.9 vs 43.9% (P = 0.006) respectively in patients and controls. The prevalence of dyslipidemia was 51.2 vs 12.1% (P = 0.09), DM was 7.3 vs 17% (P = 0.092) respectively in patients and controls. In both groups there was a significant correlation between IGF1, age, vitamin D and SBP. At the multiple regression, the greater predictor of high values of SBP were IGF1 (r = −0.75, P = 0.01; t = −2.69, P = 0.11), r = −0.18, P = 0.018 respectively). At logistic regression only in patients we found a significant association between IGF1 and vitamin D deficiency and dyslipidemia and hypertension, but not with DM. The MS was significantly associated only with vitamin D. At the multiple logistics regression, vitamin D was associated with dyslipidemia and hypertension.

In GHD hypopituitary patients the vitamin D is more associated with cardiovascular risk factors. Thus, it can be assumed that the vitamin D deficiency may present an additional risk factor to the already known effects of hypopituitarism for cardiovascular diseases.

DOI: 10.1530/endoabs.32.P169
P170

Primary hyperparathyroidism in patients with urolithiasis: prevalence and predictors
Sunil Kumar Kota¹, Lalit Kumar Meher², Shruti Jammula³ & Kirtikumar D. Modi⁴
¹Medwin Hospital, Hyderabad, Andhra Pradesh, India; ²MKCG Medical College, Berhampur, Orissa, India; ³Roland Institute of Pharmaceutical Sciences, Berhampur, Orissa, India.

Objective
To know the prevalence of primary hyperparathyroidism (PHPT) in urolithiasis and predictors of PHPT in urolithiasis.

Methods
This cross sectional study was conducted between July 2005 and July 2012 in department of endocrinology and urology at our hospital. In this study a total of 165 consecutive patients with urolithiasis with radiopaque stones were evaluated for clinical and biochemical profile. Stones retrieved were analyzed for type of stone using infrared spectroscopy.

Results
Out of these 165 patients, 123 were males, 42 females, with a mean age of 34.5 ± 12.1 years. Eleven patients (7%) had histopathologically proven PHPT. Mean age of these patients was 45.6 ± 12.4 years with male: female ratio of 4:7. Prevalence of bone pains, backache, fracture, weakness, fatigability, joint pain, and myopathy were more common in PHPT group. Three (35%) patients in PHPT and 3 (2%) in non PHPT group had nephrocalcinosis (P < 0.0001). Simultaneous renal and ureteric stones were significantly more common in PHPT patients (P < 0.0001). Calcific pancreatitis was found in 2 (18.1%) patients with PHPT as compared to 1 (0.6%) in non PHPT group (P value 0.0001). Mean serum calcium in PHPT group was 12.3 ± 0.3 g/dl vs 114.3 ± 2.6 IU/l (P<0.0001) and phosphate was 3.3 ± 0.3 vs 3.7 ± 0.5 g/dl (P value < 0.04). IPTH levels were 598.9 ± 132.4 vs 49.3 ± 3.1 pg/ml (P < 0.0001) respectively. Calcium oxalates were the most common type of stones in both of the groups (85.3 vs 69.1%) respectively.

Discussion
The prevalence of PHPT in our patient with urolithiasis is 7%. Urolithiasis is more common in males but prevalence of PHPT is more common in females with urolithiasis. Urolithiasis patients with PTH are older with additional symptomatology. Serum calcium, alkaline phosphate, parathyroid hormone levels were predictors of PHPT. Nephrocalcinosis, concomitant urteric and renal stones and calcific pancreatitis were predictors of PHPT in urolithiasis patients.

Conclusion
PHPT should be considered as an etiologic factor in urolithiasis.

DOI: 10.1530/endoabs.32.P170

P171

Could PHPT be diagnosed at early stages even more frequently?
Helena Sipiczki1, Kvetoslav Sipir2 & Zdenek Fryšák3
12nd Department of Internal Medicine, St Anne’s University Hospital Brno, Brno, Czech Republic; 2Department of Social Medicine and Health Policy, Faculty of Medicine and Dentistry, Palacky University Olomouc, Olomouc, Czech Republic; 3Department of Internal Medicine III, Nephrology, Renal and Vascular Diseases, Endocrinology and Endocrinology, Faculty of Medicine and Dentistry, Palacky University Olomouc, Olomouc, Czech Republic.

Primary hyperthyroidism (PHPT) is one of the diseases which are usually diagnosed in asymptomatic period nowadays. Even though considerable success was achieved, in some cases PHPT is not found out before complications were developed. A prospective study focuses on diagnostics and therapy of PHPT has been in progress at two tertiary centers of endocrinology in the Czech Republic since January 1st, 2007, with early diagnosis of PHPT being one of its aims. In a 6-year period, there were 217 patients with PHPT. There were 29 hypercalcemic patients. Their serum calcium level exceeded 2.60 mmol/l. 188 normocalcemic patients had serum calcium level 2.60 mmol/l or less at the first examination. Intermittent or constant hypercalcemia developed in 28 patients who were originally normocalcemic. Four years was the longest period during which constant hypercalcemia developed in an originally normocalcemic patients. Set of symptoms being characteristic of PHPT was present only in ten patients when they were included into the study group, later on some clinical features appeared in other 14 patients. The most common complaints were fatigue, gastrointestinal signs, muscular and bone pain and psychiatric problems, especially depression. There was stated a frequent coincidence of PHPT and disorders of pituitary gland. Therefore it was started with parathyroid hormone serum level examination of patients treated at the centre of endocrinology in the time of study.

Normocalcemic PHPT was found out at 107 endocrine patients.

Conclusions
Serum parathyroid hormone level examination in asymptomatic patients seems to be the most important tool of PHPT early detection. A frequent coincidence of PHPT and other endocrine disorders was found out, this finding needs to be verified. Permanent hypercalcemia can be developed in a normocalcemic patient with PHPT even after a 4-year period.

DOI: 10.1530/endoabs.32.P171

P171.1

Relation between carotid intima media thickness and vitamin D in hypertension
Bengur Taskiran, Eylem Bahadir & Ruya Mutluay
Yunus Emre State Hospital, Eskisehir, Turkey.

Introduction
Hypertension is associated with increased risk of vascular disease. There is possible relation between low vitamin D levels and subclinical atherosclerosis defined as increased carotid intima media thickness (CIMT). Vitamin D deficiency is defined as levels below 20 ng/ml. In this study we aimed to find out the relation between 25 hydroxy D vitamin level and CIMT and the presence of athrosclerotic plaques.

Methods
A total number of 163 patients (15 male and 148 female subjects) with essential hypertension aged between 30 and 76 were included to the study. The patients were already on hypertensive medication. CIMT was measured and the presence of plaque was evaluated by real time B mode ultrasonography. Serum parahormone and 25 OH vit D levels were measured using ELISA. None of the patients were on steroid medication. All parametric variables were evaluated with Student’s t-test using SPSS 10.0. The relation between 25 OH vitamin D level and CIMT was evaluated with Pearson correlation analysis. χ² test was done for nonparametric variables. P value below 0.05 was considered statistically significant.

Results
Patients with plaques were older than those without plaques (P = 0.0001) and had longer duration of hypertension (P = 0.008) and higher TSH level (P = 0.06).

Eighty had plaques. Seventy three patients had severe vitamin D deficiency defined as level below 10 ng/ml and 64 had insufficiency, (10–20 ng/ml). Vitamin D levels were similar in both groups (P = 0.44) but those with plaques had higher CIMT (P = 0.0001). CIMT was positively correlated with age (r = 0.399, P = 0.0001), fasting glucose (r = 0.165, P = 0.036), and HbA1c (r = 0.384, P = 0.002). There was no correlation between Vitamin D level (P = 0.75) and LDL (P = 0.581).

Conclusion
We did not find any relation between vitamin D level and CIMT in hypertensive subjects. The lack of significance may be due to high prevalence of vitamin D deficiency. There was no correlation between vitamin D level (P = 0.75) and LDL (P = 0.581).

DOI: 10.1530/endoabs.32.P171.1

Cardiovascular Endocrinology & Lipid Metabolism

P172

Lipid levels in acromegaly
Ifigenia Kostoglou-Athanassiou1, Anastasios Gkountouvas2, Ioannis Keramidas3, Eleni Xanthakou1, Fotini Chatjimarkou2 & Philippos Kalymidis1
1Department of Endocrinology, Red Cross Hospital, Athens, Greece; 2Department of Endocrinology, Metaxa Hospital, Piraeus, Greece; 3Endocrinologist, Athens, Greece.

Acromegaly is known to be associated with increased cardiovascular risk. Additionally, acromegaly is known to be associated with disordered carbohydrate metabolism. Lipid levels in acromegaly have not been extensively studied. The aim was to study lipid levels in acromegaly.

Methods
In 32 patients with newly diagnosed acromegaly lipid levels were studied. In particular total cholesterol, HDL cholesterol, LDL cholesterol and triglyceride levels were measured. All patients had a pituitary adenoma. All of them had increased IGF1 levels. The measurements were also performed in 32 control subjects matched for age and sex.
Results
Total cholesterol was 220.59 ± 8.24 mg/dl (mean ± S.E.M.) in patients with acromegaly as opposed to 198.55 ± 4.85 mg/dl in the control subjects (p < 0.001). Student’s i-test). HDL cholesterol levels were 52.96 ± 2.89 mg/dl in patients with acromegaly as opposed to 58.44 ± 5.62 mg/dl in the control group (p < 0.001). LDL cholesterol was 151.70 ± 13.77 mg/dl in the acromegalic patients as opposed to 114.06 ± 5.31 mg/dl in the control group (p < 0.001), Triglyceride levels were 140.34 ± 14.79 mg/dl in patients with acromegaly as opposed to 133.50 ± 14.27 mg/dl in the control group (p < 0.001). Thus, total cholesterol, LDL cholesterol and triglyceride levels were increased in patients with acromegaly as opposed to the control group, while HDL cholesterol was decreased.

Conclusions
It appears that acromegaly is associated with a proatherogenic lipid profile, which may contribute to the increased cardiovascular risk associated with the disease.

DOI: 10.1530/endoabs.32.P172

P173
Testosterone stimulates cholesterol metabolism and efflux from human macrophages via liver X receptor
Elizabeth Kelby1, Hugh Jones3
1Department of Human Metabolism, Medical School, University of Sheffield, Sheffield, UK; 3Diabetes and Endocrinology, Barnsley Hospital NHS Foundation Trust, Barnsley, UK.

Low testosterone is associated with an increased prevalence of cardiovascular (CV) disease. Testosterone replacement improves several CV risk factors including lowering cholesterol and may protect against atherosclerosis. Macrophage liver X receptor (LXR) is a nuclear receptor which regulates lipid and glucose metabolism. LXR agonists protect against atherosclerosis but may have hepatic complications. We investigated LXR expression and key downstream targets involved in lipid and glucose metabolism in liver, muscle and adipose tissue of the testicular feminised mouse (Tfm) which exhibit non-functional androgen receptors (AR) and low circulating testosterone levels. This study investigated LXR expression and key downstream targets involved in lipid and glucose homeostasis in liver, muscle and adipose tissue of Tfm mice. It was therefore proposed that the anti-atherogenic effect of testosterone may be mediated via LXR as a therapeutic target for the treatment of atherosclerosis. It was therefore proposed that the anti-atherogenic effect of testosterone may be mediated via LXR as a therapeutic target for the treatment of atherosclerosis. We used a high fat diet fed to Tfm mice and control wild-type mice (WT) to investigate LXR expression and key downstream targets involved in lipid and glucose metabolism (peroxisome proliferator-activated receptors (PPARα, PPARγ) and sterol regulatory element-binding proteins (SREBP1c, SREBP2)).

In this study, testosterone supplementation was shown to increase the expression of LXRα but not LXRβ in liver, muscle and adipose tissue of Tfm mice. Furthermore, testosterone increased the expression of downstream targets involved in lipid metabolism (acetyl coA carboxylase (ACC), fatty acid synthase (FAS), lipoprotein lipase (LPL), apolipoprotein E (ApoE), and ATP-binding cassette transporters (ABC-A1, ABC-G5)) in liver, muscle and adipose tissue of Tfm mice. These findings suggest that testosterone may stimulate hepatic LXR expression and downstream targets involved in lipid and glucose metabolism in the liver, muscle and adipose tissue of Tfm mice, which may contribute to the anti-atherogenic effect of testosterone. However, further studies are required to investigate the mechanism of action of testosterone on LXR expression and downstream targets in liver, muscle and adipose tissue of Tfm mice.

DOI: 10.1530/endoabs.32.P174

P175
Oxytocin, a new regulator of cardiomyocyte hypertrophy
Jolanta Gutkowska1,2, Ahmed Menaouar1 & Marek Jankowski1,2
1CR-CHUM, Montreal, Quebec, Canada; 2Department of Medicine, University of Montreal, Montreal, Quebec, Canada.

We have uncovered the cardioprotective functional oxytocin (OT) system in the rat and human heart. In rat model of heart infarct, OT treatment significantly reduced infarct size, decreased cardiomyocytes (CM) diameter, increased expression of atrial natriuretic peptide (ANP) and improved parameters of heart function. Consequently, in this report we investigated hypothesis that OT-related mechanism of ANP synthesis or release, plays a role in the control of CM hypertrophy.

The experiments were carried out in culture of newborn and adult rat CM in which we observed that OT treatment significantly reduced CM hypertrophy induced by other stressors, such as angiotensin II and phenylephrine. OT dose-dependently increased ANP release and cGMP concentrations in newborn rat CM. However, the ANP receptor blockade by anatin did not completely inhibited cGMP enhancement in CM exposed to OT suggesting also contribution of NO. Indeed, OT-mediated cGMP enhancement in CM was reduced by L-NAME, a non-specific inhibitor of NO synthases, partially reduced by 1400 W, an inhibitor of inducible NOS, and ODQ, an inhibitor of NO-sensitive guanylyl cyclases. Sildenafil reduced cGMP inhibition of anti-hypertrophic OT effects in CM indicated also the contribution of calcium–calmodulin kinase kinase and AMP-activated protein kinase pathways. ANP modulation of OT and NO signaling cascades. CM exposed to OT significantly enhanced CM growth compared to control CM. Nevertheless, OT did not affect CM growth in presence of L-NAME, suggesting that OT-mediated CM growth was dependent on NO synthesis.

In conclusion, we have uncovered the cardioprotective functional OT system in the rat and human heart. OT treatment significantly reduced infarct size, decreased cardiomyocytes (CM) diameter, increased expression of atrial natriuretic peptide (ANP) and improved parameters of heart function. We have uncovered the cardioprotective functional oxytocin (OT) system in the rat and human heart. In rat model of heart infarct, OT treatment significantly reduced infarct size, decreased cardiomyocytes (CM) diameter, increased expression of atrial natriuretic peptide (ANP) and improved parameters of heart function. Consequently, in this report we investigated hypothesis that OT-related mechanism of ANP synthesis or release, plays a role in the control of CM hypertrophy.

The experiments were carried out in culture of newborn and adult rat CM in which we observed that OT treatment significantly reduced CM hypertrophy induced by other stressors, such as angiotensin II and phenylephrine. OT dose-dependently increased ANP release and cGMP concentrations in newborn rat CM. However, the ANP receptor blockade by anatin did not completely inhibited cGMP enhancement in CM exposed to OT suggesting also contribution of NO. Indeed, OT-mediated cGMP enhancement in CM was reduced by L-NAME, a non-specific inhibitor of NO synthases, partially reduced by 1400 W, an inhibitor of inducible NOS, and ODQ, an inhibitor of NO-sensitive guanylyl cyclases. Sildenafil reduced cGMP inhibition of anti-hypertrophic OT effects in CM indicated also the contribution of calcium–calmodulin kinase kinase and AMP-activated protein kinase pathways. ANP modulation of OT and NO signaling cascades. CM exposed to OT significantly enhanced CM growth compared to control CM. Nevertheless, OT did not affect CM growth in presence of L-NAME, suggesting that OT-mediated CM growth was dependent on NO synthesis.

In conclusion, we have uncovered the cardioprotective functional OT system in the rat and human heart. OT treatment significantly reduced infarct size, decreased cardiomyocytes (CM) diameter, increased expression of atrial natriuretic peptide (ANP) and improved parameters of heart function. We have uncovered the cardioprotective functional OT system in the rat and human heart. OT treatment significantly reduced infarct size, decreased cardiomyocytes (CM) diameter, increased expression of atrial natriuretic peptide (ANP) and improved parameters of heart function. Consequently, in this report we investigated hypothesis that OT-related mechanism of ANP synthesis or release, plays a role in the control of CM hypertrophy.

The experiments were carried out in culture of newborn and adult rat CM in which we observed that OT treatment significantly reduced CM hypertrophy induced by other stressors, such as angiotensin II and phenylephrine. OT dose-dependently increased ANP release and cGMP concentrations in newborn rat CM. However, the ANP receptor blockade by anatin did not completely inhibited cGMP enhancement in CM exposed to OT suggesting also contribution of NO. Indeed, OT-mediated cGMP enhancement in CM was reduced by L-NAME, a non-specific inhibitor of NO synthases, partially reduced by 1400 W, an inhibitor of inducible NOS, and ODQ, an inhibitor of NO-sensitive guanylyl cyclases. Sildenafil reduced cGMP inhibition of anti-hypertrophic OT effects in CM indicated also the contribution of calcium–calmodulin kinase kinase and AMP-activated protein kinase pathways. ANP modulation of OT and NO signaling cascades. CM exposed to OT significantly enhanced CM growth compared to control CM. Nevertheless, OT did not affect CM growth in presence of L-NAME, suggesting that OT-mediated CM growth was dependent on NO synthesis.
P176
Long QT interval in Turner syndrome: a high prevalence of LQTS gene mutations
Christian Trolle1, Kristian Havmand Mørtensen1,2, Lisbeth Nørregaard Pedersen1, Henrik Kjørrild Jensen4, Niels Holm Andersen4 & Claus Højbjerg Gravholt1,2
1Medical Research Laboratories, Department of Endocrinology and Internal Medicine, Aarhus, Denmark; 2Department of Radiology, Cambridge University Hospitals, Cambridge, UK; 3Department of Molecular Medicine, Aarhus University Hospital, Aarhus, Denmark; 4Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark.

Objective
QT interval prolongation of unknown aetiology is common in Turner syndrome (TS). This study set out to explore the presence of known pathogenic long QT (LQT) mutations in TS and to examine the corrected QT interval (QTC) over time and relate the findings to the TS phenotype.

Methods
Adult females with TS (n=102) were examined thrice with a mean follow-up of 4.7 ± 0.5 years, and 68 age-matched healthy controls were examined once. QT was measured by one blinded reader (intra-reader variability: 0.7%), and adjusted for influence of heart rate by Bazett’s (QTC) and Hodges’s formula (hQTC). The prevalence of mutations in genes related to Long QT syndrome (LQTS) was determined in females with TS and a QTC >432.0 ms. Echocardiographic assessment of aortic valve morphology, 24-h blood pressures and blood samples were done.

Results
The mean hQTC in females with TS (414.0 ± 25.5 ms) compared to controls (390.4 ± 17.8 ms) was prolonged (P < 0.001) and did not change over time (416.9 ± 22.6 vs 415.6 ± 25.5 ms; P=0.4). 45,X karyotype was associated with increased hQTC prolongation compared to other TS karyotypes (418.2 ± 24.8 vs 407.6 ± 25.5 ms; P=0.03). In females with TS and a QTC >432 ms, seven bad mutations in major LQTS-genes (SCN5A and KCN2) were noted in one of the minor LQTS-gene (KCNE2).

Conclusion
The prevalence of mutations in major LQTS genes was strikingly high for females with TS and the longest QTC interval.

DOI: 10.1530/endoabs.32.P176

P177
Osteoprotegerin and RANKL levels in stable coronary artery disease
Camelia Guraian1, Melania Balas3, Daniela Amzar1, Ioana Golu1, Loredana Stan1 & Ioana Zosin2
1Department of Biochemistry, V. Babes University of Medicine and Pharmacy, Timisoara, Romania; 2Department of Endocrinology, V. Babes University of Medicine and Pharmacy, Timisoara, Romania; 3Department of Anatomy and Embriology, V. Babes University of Medicine and Pharmacy, Timisoara, Romania.

Introduction
Osteoprotegerin (OPG) and receptor activator for nuclear factor-κB ligand (RANKL) are cytokines that increase in cardiovascular calcifications, while RANKL is expressed by atherosclerotic lesions. The aim of the study was to assess the OPG and RANKL concentrations in patients with stable coronary artery disease.

Material and methods
The study included 38 patients diagnosed with ischemic coronary disease (16 men and 22 women, mean age 54.3 ± 7.2 years) and 34 control subjects, sex and age-matched. Analyses for serum cholesterol, high and low-density lipoprotein (HDL and LDL) cholesterol, triglycerides, and glucose were performed by enzymatic methods. High-sensitivity C-reactive protein (hsCRP), OPG and RANKL were measured by ELISA.

Results
Serum OPG levels were significantly higher in study group than in controls (3.52 ± 0.75 vs 1.19 ± 0.35 pmol/l, P < 0.0001). RANKL (pmol/l) to OPG (pmol/l) ratio was significantly higher in study cases than in controls (0.48 ± 0.12 vs 0.30 ± 0.12, P < 0.0001). OPG values did not correlate with age, cholesterol, HDL-cholesterol, triglycerides and hsCRP. A significant correlation was found between RANKL and OPG: r=0.530, r²=0.281, P=0.003, RANKL/OPG correlated positively with total cholesterol (r=0.509, r²=0.295, P=0.004) and hsCRP values (r=0.453, r²=0.205, P=0.01), but it didn’t correlate with age, triglycerides and glucose. There were no significant differences between men and women regarding: OPG, RANKL/OPG, hsCRP levels and lipid profile. Receiver-operating curve analysis showed that at a cutoff point of 0.381, RANKL/OPG presented a sensitivity of 86.2%, but a lower specificity (76.6%). At a cutoff point of 2.52 pmol/l, OPG showed a better sensitivity (91.2%) and specificity (89.1%). At a cutoff point of 2.95 mg/l, hsCRP presented a moderate sensitivity (79.3%), but a good specificity (93.1%).

Conclusion
Our study confirms that OPG and RANKL/OPG values are higher in ischemic patients, correlated with other inflammatory markers (hsCRP). RANKL/OPG could represent a good assessment and prediction parameter of future cardiac events.

DOI: 10.1530/endoabs.32.P177

P178
Intestinal cholesterol-transport gene expression is associated with abnormalities in post-prandial endothelial function and carotid intima-media thickness independent of insulin resistance
W Matthew Widdowson1, Anne McCowan1, James Phelan1, Gerard Boran2, John Reynolds1 & James Gibney1
1Endocrinology Department, Tallaght Hospital, Dublin, Ireland; 2Department of Chemical Pathology, Tallaght Hospital, Dublin, Ireland; 3Department of Surgery, St James’s Hospital, Dublin, Ireland.

Introduction
Intestinal cholesterol absorption is known to be important in post-prandial lipid levels, and implicated in the development of vascular disease. This study evaluated the effect of intestinal gene expression on markers of early vascular disease in a cohort of diabetic and non-diabetic subjects.

Methods
Subjects were identified from routine upper GI lists and enrolled as per local ethics approval. Intestinal gene expression was measured on duodenal biopsy samples, using rtPCR to measure mRNA levels of Niemann-Pick C1-L1, ABCG5, ABCG8, ABCA1, microsomal transport protein (MTTP), and sterol regulatory element-binding protein types 1 and 2. Following a standard mixed meal, serum lipid profiles were measured and insulin resistance was measured via HOMA-IR. Post-prandial endothelial function was assessed via flow-mediated dilatation (FMD) of the brachial artery, and carotid IMT measured using B-mode ultrasonography. Statistical analysis utilised SPSS (Ver 10.1).

Results
One hundred patients were analysed. Intestinal gene expression was associated with alterations in IMT and post-prandial FMD as demonstrated in Table 1, corrected for age, BMI and HOMA-IR. Pasting and post-prandial lipid levels were not associated with either vascular markers or intestinal gene expression. Gene expression was not affected by smoking status, diabetic staus or gender.

Table 1

<table>
<thead>
<tr>
<th>Gene</th>
<th>NPC1L1</th>
<th>ABCG5</th>
<th>ABCG8</th>
<th>MTTP</th>
<th>ABCA1</th>
<th>SREBP1</th>
<th>SREBP2</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMT</td>
<td>0.147*</td>
<td>0.349*</td>
<td>0.324*</td>
<td>0.274*</td>
<td>0.229*</td>
<td>0.078*</td>
<td>0.296*</td>
</tr>
<tr>
<td>FFMD</td>
<td>-0.245*</td>
<td>-0.197*</td>
<td>-0.246*</td>
<td>-0.293*</td>
<td>-0.358*</td>
<td>-0.363*</td>
<td>-0.287*</td>
</tr>
</tbody>
</table>

*P<0.05, †P<0.01, ‡NS. Values are for R (Pearson’s correlation coefficient).

Conclusion
Intestinal gene expression shows significant association with increased IMT, a marker for early atherosclerotic change, as well as reduced post-prandial FMD, a marker of early endothelial dysfunction. This association appears to be independent of post-prandial lipid levels and glycemic status.

DOI: 10.1530/endoabs.32.P178

Endocrine Abstracts (2013) Vol 32
P179
Mediterranean diet modulates the effect of rs1761667 in the CD36 gene on FFA concentration and BMI in a high cardiovascular risk population
Carolina Ortega-Azorín1, Diego Godoy1,2, Paula Carrauso1, Eva M Asensio1, Vicente Zazo-Mortera1, Dolores Corella1 & Jose V Stolz1,2
1Department of Preventive Medicine and CIBER Fisiopatología de la Obesidad y Nutrición, University of Valencia, Valencia, Spain; 2University General Hospital, Valencia, Spain.

Introduction and objective
CD36 is a scavenger receptor that facilitates the membrane transport of long chain fatty acids into muscle and adipose tissue. Polymorphisms in this gene have been related to abnormal serum fatty acids and obesity-related phenotypes with inconsistent results. Gene-diet interactions could modulate these associations. Our aim was to study whether a common functional variant (rs1761667) in this gene will associate with anthropometric variables and plasma free fatty acids (FFA) as well as the modulation by the adherence to the Mediterranean diet (MD) in a high cardiovascular risk (CVR) population.

Material and methods
We studied 1036 subjects with high CVR participating in the PREVIMED (PREVención Diet MDeritratónea) study, recruited in Valencia. Anthropometric data was obtained and plasma FFA were determined. Adherence to MD was evaluated through a validated questionnaire. Individuals were classified according to the score: low adherence (<9 points) or high adherence (≥9 points).

Results
Minor allele frequency (G) was 0.427. A recessive model was considered (A-allele carriers vs GG homozygous). Homozygous GG subjects had higher FFA concentrations than carriers of the A allele (GG: 18.9±7.8 mg/dl vs AA+AG: 17.4±6.7 mg/dl, P=0.035). Interestingly, we observed an interaction (P-int: 0.049) between rs1761667 polymorphism and adherence to the MD in determining FFA concentrations (P-int:0.049) and BMI (P-int:0.019). So, in subjects with low adherence to MD, the GG genotype showed higher FFA concentrations (GG: 20.3±7.8 mg/dl vs AA+AG: 17.5±6.4 mg/dl, P=0.001), and BMI (GG: 32.1±5.6 kg/m² vs AA+AG: 31.0±5.0 kg/m², P=0.046) compared with A-allele carriers. But, in subjects with high adherence to MD no significant differences were observed according to genotype in this parameters (FFA, P=0.702; BMI, P=0.555).

Conclusion
Adherence to MD modulates the effect of the CD36-rs1761667 polymorphism on FFA concentration and BMI in a high CVR population.

DOI: 10.1530/endoabs.32.P179

P180
The effect of aerobic exercise on ectopic lipids intramyocellular, intrahepatocellular, and intracardiomyocellular lipids in physically active, healthy individuals
Marion Krues1, Julie Bacher1, Roland Kreis2, Michael Ihl2, Thomas Zueger1, Christoph Sterzel1, Chris Boesch2 & Emanuel Christ1
1Division of Endocrinology, Diabetology and Clinical Nutrition, University Hospital of Bern, Inselspital, Bern, Switzerland; 2Departments of Clinical Research and Radiology, University of Bern, Bern, Switzerland.

Introduction
Ectopic lipids are fuel stores in non-adipose tissues (i.e. skeletal muscle (IMCL), liver (IHCL), and heart (ICCL)). It is recognized that IMCL can be depleted by physical activity and replenished by dietary fat intake indicating metabolic flexibility. In contrast, preliminary data suggested that aerobic exercise increases IHCL. Data on the acute effect of aerobic exercise on ICCL is scarce. Increased IMCL and IHCL have consistently been related to impaired insulin sensitivity and visceral/subcutaneous fat mass or HOMA-index. These results underscore the fact that all ectopic lipids are flexible fuel stores that are influenced by physical exercise.

In this homogenous group, physical exercise consistently decreased both ICCL and IMCL and increased IHCL.

DOI: 10.1530/endoabs.32.P180

P181
Can hypothyroidism manifest as ischemic heart disease in elderly patients with the absence of significant coronary atherosclerosis?
Elena Yaroslavskaya1, Vadim Kuznetsov1, Maurizio Parato1,2, Dmitry Krinochkin1, Georgyi Pushkarev1 & Elena Gorbatenko1
1Tyumen Cardiology Center, Tyumen, Russia; 2Madonna del Soccorso Hospital and Politecnica delle Marche University, San Benedetto del Torno, Italy.

In elderly patients with symptoms of ischemic heart disease (IHD) coronary angiography often fails to reveal significant atherosclerosis. The causes of the absence of significant coronary atherosclerosis (SCA) in these patients have not been determined.

Purpose
To determine predictors of SCA absence in the elderly IHD patients.

Methods
This is a retrospective study of consecutive 10 713 patients who underwent coronary angiography at the Tyumen Cardiology Centre in 1991–2011. We selected 1483 patients with IHD and without SCA: 124 patients 65 years old and older (group I) and 1 359 patients younger than 65 years (group II).

Results
In patients of group I the incidence of hypothyroidism was higher and incidence of myocardial infarction (MI) was lower compared to group II. Echocardiographic indices of left ventricular (LV) posterior wall thickness, aortic root and left atrium in group I patients were higher. LV diastolic dysfunction was more frequent in patients of group I. According to the results of multivariate analysis LV diastolic dysfunction (OR=2.64; 95% CI 1.21–5.77; P=0.001), hypothyroidism (2.35; 1.45–3.81; 0.015), increased indices of LV posterior wall thickness (1.67; 1.45–3.81; 0.019), left atrium (1.31; 1.09–2.55; 0.002), aortic root (1.26; 1.11–1.55; 0.006) and the absence of prior MI (0.34; 0.15–0.79; 0.011) were independent predictors of the SCA absence in elderly patients with IHD.

Conclusions
Hypothyroidism was strong independent predictor of the SCA absence in elderly IHD patients. Hypothyroidism as a cause of microvascular myocardial dysfunction could manifest clinically as IHD in elderly patients with the absence of SCA.

DOI: 10.1530/endoabs.32.P181

P182
Short-term changes in serum sex steroid levels and cardiac function in healthy young men
Maarten De Smet1,2, Bruno Lapauw1, Tine De Backer1 & Johannes Ruige1
1Department of Endocrinology, Ghent University Hospital, Ghent, Belgium; 2Department of Cardiology, Ghent University Hospital, Ghent, Belgium.

Introduction
Male obesity is associated with an increase in estradiol (E2) and a decrease in testosterone (T). And, although sex steroids are associated with cardiovascular disease, direct effects on cardiac structure and function are hardly investigated in humans.

Methodology
Twenty healthy men aged 20–40 years were randomized into two groups. One group was given an aromatase inhibitor (letrozole) only, thus obtaining a high paired t-tests. Correlations between relative changes in these lipids and insulin sensitivity and visceral/subcutaneous fat mass were evaluated.

Results
A 2 h-exercise resulted in a significant decrease in IMCL (~17±22%, P=0.008) and ICCL (~17±14%, P=0.002) and an increase in IHCL (42±29%, P=0.004). In this cohort no significant correlations were found between the relative changes in IMCL, ICCL, and fat mass or HOMA-index.

Conclusions
These results underscore the fact that all ectopic lipids are flexible fuel stores that are influenced by physical exercise.
In young healthy men, an increase in E2 and decrease in testosterone levels during the 10-year follow-up. To overcome problems of residual confounding, parameters; and prospectively with all-cause mortality (277 deaths, 14.7%) testosterone concentrations were cross-sectionally associated with cardiometabolic risk factors and mortality, suggesting that previously reported associations might always exceed the normal range. 2D STE revealed significantly decreased GLS (−17.15±2.7 vs −19.3±3.3, P<0.001), and GCS (51.2±17 vs −18.8±3.24, P=0.002), with similar GRS. In addition, GHD had decreased values for systolic, early and late diastolic SR (SrEs, SrRs, and SRi); when compared to normal subjects (−0.9±0.4 vs −1.1±0.2, P=0.016; 1.15±0.4 vs 1.31±0.3, P=0.027; 0.71±0.19 vs 0.96±0.21, P<0.001). They also had lower RotB (−4.78±2.6 vs −6.2±2.1, P=0.003), LV torsion (1.8±0.6 vs 2.3±1.1, P=0.011), TR (92.8±30 vs 121±52, P=0.002), and UTR (99±36 vs −132±47, P<0.001), but similar apical rotation. Arterial and endothelial function parameters were similar between groups. While troponin I was normal in all patients, prodBNP levels were significantly increased in the GHD group.

Conclusion GHD patients have subclinical LV systolic and diastolic dysfunction, best revealed by STE, associated with increased prodBNP levels and correlates to the level of GH deficiency (r=0.614, P<0.001). Our findings suggest that patients with GHD have intrinsic myocardial disease, probably due to insufficient contractile function of the myocardial fibres.

DOI: 10.1530/endobs.32.P184

Mechanism of oxytocin-mediated cardiomyocyte protection
Marek Jankowski1,2, Araceli Gonzalez-Reyes1 & Jolanta Gutkowska1,2
1CR-CHUM, Montreal, Quebec, Canada; 2Department of Medicine, University of Montreal, Montreal, Quebec, Canada.

Oxytocin (OT) treatment improves heart functional recovery in rat model of myocardial infarct. We investigated in the H9c2 cell line (cardiomyocytes model), mechanism of OT action in simulated ischemia - reperfusion (sI-R), H9c2 cells were suspended in warm ischemic buffer and placed inside an anoxic chamber for 2 h at 37 °C, then ‘reperfused’ under normal nutrients and oxygen conditions for 2 h. OT presence during ischemia increased cell viability by 9.7±2.5% (P<0.05) and OT at reperfusion increased cell viability further by 15.8±3.5% (P<0.001) as measured by MTT cell proliferation assay, OT treatment before ischemia had no effect. The significant cellular protection started at a concentration of 1 nM of OT, with an optimal protection at 62.5–125 nM. OT antagonist dose-dependently blocked the protective effect of OT. OT treatment of H9c2 cells transfected with OT receptor (OTr) siRNA increased cell apoptosis threefold in comparison to the control. OT increase in cell mortality in OTr siRNA cells could be mediated by vasoressin (AVP) receptors. Indeed, blockade

DOI: 10.1530/endobs.32.P185

Adults with GH deficiency have subclinical longitudinal left ventricular dysfunction, without significant vascular function impairment, suggesting intrinsic myocardial disease
Corin Badiu1, Sorina Mihaila1, Raluca Mincu2, Ruxandra Dobrescu1 & Dragos Vinereanu1
1National Institute of Endocrinology, Bucharest, Romania; 2University Hospital, Bucharest, Romania; 3Davila University of Medicine and Pharmacy, Bucharest, Romania.

Aims GH deficiency (GHD) is associated with increased cardiovascular events. We aimed to evaluate cardiac, arterial, and endothelial function, by conventional and 2D speckle tracking echocardiography (STE), and biomarkers (prodBNP and troponin I), in GHD patients by comparison with normal individuals with similar cardiovascular risk profile.

The study included 52 GHD patients (46.9±15.6, 36 males), free of cardiovascular disease, severe hypertension or diabetes and 50 normals (N). Global LV systolic function was assessed from LV fractional shortening (FS), LV ejection fraction (LVFEF, MAPSE, and cardiac index (CI). By STE, longitudinal LV function was assessed from: global longitudinal systolic strain (GLS), global longitudinal systolic, early and late diastolic strain rate (SrEs, SrRs, and SRi); radial function from global radial strain (GRS); circumferential function from global circumferential strain (GCS); and LV torsion from basal (RotB) and apical rotation (RotA), LV torsion (LVtor), twist rate (TR) and untwist rate (UTR).

Arterial function was assessed from intima-media thickness (IMT), local wave speed (LWS), Peterson elastic modulus, and stiffness index (β); endothelial function from flow mediated dilatation (FMD).

Results In GHD patients, conventional systolic LV parameters were significantly decreased compared to N (FS: 28±8 vs 38.6±7.3; LVFEF: 54±8 vs 66±8; MAPSE: 12±2 vs 16±2; CI: 2.1±0.75 vs 2.7±0.77, all P<0.001), but did not always exceed the normal range. 2D STE revealed significantly decreased GLS (−17.15±2.7 vs −19.3±3.3, P<0.001), and GCS (51.2±17 vs −18.8±3.24, P=0.002), with similar GRS. In addition, GHD had decreased values for systolic, early and late diastolic SR (SrEs, SrRs, and SRi); when compared to normal subjects (−0.9±0.4 vs −1.1±0.2, P=0.016; 1.15±0.4 vs 1.31±0.3, P=0.027; 0.71±0.19 vs 0.96±0.21, P<0.001). They also had lower RotB (−4.78±2.6 vs −6.2±2.1, P=0.003), LV torsion (1.8±0.6 vs 2.3±1.1, P=0.011), TR (92.8±30 vs 121±52, P=0.002), and UTR (99±36 vs −132±47, P<0.001), but similar apical rotation. Arterial and endothelial function parameters were similar between groups. While troponin I was normal in all patients, prodBNP levels were significantly increased in the GHD group.

Conclusion GHD patients have subclinical LV systolic and diastolic dysfunction, best revealed by STE, associated with increased prodBNP levels and correlates to the level of GH deficiency (r=0.614, P<0.001). Our findings suggest that patients with GHD have intrinsic myocardial disease, probably due to insufficient contractile function of the myocardial fibres.

DOI: 10.1530/endobs.32.P184

P185

Mendelian randomization suggests non-causal associations of testosterone with cardiometabolic risk factors and mortality
Robin Haring, Alexander Teumer, Uwe Volker, Marcus Dörr, Matthias Nauck, Reiner Biffar, Henry Völzke, Sebastian Baumeister & Henri Wallaschöfl
University Medicine Greifswald, Greifswald, Germany.

Background Prospective studies showed that low serum testosterone concentrations are associated with various cardiometabolic risk factors and mortality. But the causal nature of these associations is controversial.

Methods We studied 1882 men aged 20–79 years with serum testosterone concentrations and genotyping data from the longitudinal population-based Study of Health in Pomerania.

Testosterone concentrations were cross-sectionally associated with cardiometabolic risk factors including anthropometric, lipid, blood pressure, and glycemic parameters; and prospectively with all-cause mortality (277 deaths, 14.7%) during the 10-year follow-up. To overcome problems of residual confounding, reverse causation, or regression dilution bias in the investigated testosterone-outcome associations, we used two-stage least square regression models with previously identified polymorphisms at the 3SHBG gene (rs12150660) and X chromosome (rs5934505) as multiple genetic instruments in an instrumental variable (IV) approach, also known as Mendelian randomisation.

Results In standard regression analyses, testosterone was robustly associated with a wide range of cardiometabolic risk factors. In subsequent IV analyses, no such significant associations were observed. Similarly, prospective analyses showed a consistent association of low testosterone concentrations with increased all-cause mortality risk, which was not apparent in subsequent IV analyses.

Conclusion The present Mendelian randomization analyses did not detect any evidence for causal associations of testosterone concentrations with cardiometabolic risk factors and mortality, suggesting that previously reported associations might largely result from residual confounding or reverse causation. Although testosterone assessment might improve risk prediction, implementation of testosterone replacement therapy requires further evidence of a direct effect on cardiometabolic outcomes from double-blinded randomized controlled trials and large-scale Mendelian randomization meta-analyses.

DOI: 10.1530/endobs.32.P183
of AVP receptors by conivaptan increased cell viability in sI-R conditions. OT treatment reduced fluorescence of CM-H2DCFDA products in sI-R-treated cells indicating decrease of reactive oxidative species (ROS). Interestingly, these experiments revealed that under normoxic conditions, OT treatment alone is sufficient to trigger a short-lived burst in intracellular ROS. The OT protection of sI-R was blocked by the PI3K–Akt inhibitor, Wortmannin. Using confocal microscopy, we noted that cells treated with OT displayed increased Akt (Thr308) phosphorylation and specifically, Akt was accumulated in ring-like structures associated with mitochondria and nuclei. Demonstration that KT5823, inhibitor of protein kinase G (PKG) and ODQ, inhibitor of soluble guanylyl cyclase, reduced OT-mediated protection in sI-R, indicated the role of cGMP-dependent protein kinase. Consequently, the confocal microscopy demonstrated the increase of eNOS phosphorylation and its nuclear accumulation in cells treated with OT. OT protection in sI-R was also inhibited by ANP receptor antagonist, A71915. These data suggest that OT provides protection to the injured heart protein kinase. Consequently, the confocal microscopy demonstrated the increase of protein kinase G (PKG) and ODQ, inhibitor of soluble guanylyl cyclase, reduced OT-mediated protection in sI-R, indicated the role of cGMP-dependent protein kinase. Consequently, the confocal microscopy demonstrated the increase of eNOS phosphorylation and its nuclear accumulation in cells treated with OT. OT protection in sI-R was also inhibited by ANP receptor antagonist, A71915. These data suggest that OT provides protection to the injured heart indicating decrease of reactive oxidative species (ROS). Interestingly, these data suggest that OT provides protection to the injured heart indicating decrease of reactive oxidative species (ROS).

**P186**

The effect of testosterone replacement on endothelial dysfunction, inflammation and insulin resistance in male hypogonadotrophic hypogonadism

Alper Sonmez1, Abdullah Taslipinar1, Aydogan Aydogdu1, Serkan Tapan2, Coskun Meric1, Yalcin Basaran1, Erdim Sertoglu1, Mahmut I Yilmaz1, Muhittin A Serdar1, Taner Ozgurias1, Erol Bulu1 & Mustafa Kutlu1
1Department of Endocrinology and Metabolism, School of Medicine, Gulhane Military Medical Academy, Ankara, Turkey; 2Department of Clinical Biochemistry, School of Medicine, Gulhane Military Medical Academy, Ankara, Turkey; 3Department of Nephrology, School of Medicine, Gulhane Military Medical Academy, Ankara, Turkey.

**Objective**

Metabolic disorders are common in patients with hypogonadism. Testosterone replacement therapy (TRT) significantly improves symptoms of testosterone deprivation such as mood, libido or musculoskeletal power. However, whether the metabolic and cardiovascular risk is improved is not clearly known. We aimed to search for the metabolic and cardiovascular effects of TRT.

**Design**

Prospective study, performed in the outpatient units of Gulhane Military Medical School.

**Methods**

Treatment naive young patients with congenital hypogonadotropic hypogonadism (CHH; n=80, mean age 21.56 ± 2.1 years) were treated with either testosterone ene (250 mg/3 weeks i.m.; n = 59) or testosterone transdermal gel (50 mg daily; n = 21) in a mean follow-up period of 6.0 ± 2.4 months. The demographic parameters, fasting glucose, insulin, pentaxin 3 (PTX3) and asymmetric dimethyl arginine (ADMA) levels were measured both before and after treatment periods. The insulin sensitivity was estimated by HOMA-IR formula.

**Results**

The BMIs and waist circumferences were increased (P < 0.001 and P = 0.001 respectively) and the total and HDL cholesterol levels were decreased (P = 0.002 and P < 0.001 respectively) after the follow-up period. Both plasma ADMA and PTX-3 levels were increased (P < 0.001 and P = 0.02 respectively) while there were no significant alterations in the HOMAIR values. The alterations were similar in two different TRT regimens.

**Conclusions**

The study shows that, both daily transdermal and periodic injectable modalities worsen the surrogate markers of endothelial dysfunction and inflammation in young and treatment naive subjects with CHH. Randomized prospective cohorts are warranted to see whether these short term unfavorable results will affect cardiometabolic outcomes of these patients.

**P187**

**P187**

**TSH and arterial stiffness in healthy postmenopausal women**

Eleni Armeni1, Kimon Stamateopoulos2, Georgios Georgiopoulos3, Maria Kazani4, Andreas Alexandrou4, Efthimios Deligeorgoul5, Alexandra Livada6, Charalampos Psychas7, Maria Creatsas8, George Bouboulis5 & Irene Lambrinoudaki1
12nd Department of Obstetrics and Gynecology, Aretaieio Hospital, National and Kapodistrian University of Athens, Athens, Attiki, Greece; 2Department of Therapeutics, Alexandra Hospital, National and Kapodistrian University of Athens, Athens, Attiki, Greece; 3Hormonal Laboratory, Aretaieio Hospital, National and Kapodistrian University of Athens, Athens, Attiki, Greece; 4Department of Statistics, Athens University of Economics and Business, Athens, Attiki, Greece.

**Introduction**

Thyroid dysfunction, whether overt or subclinical, has a significant effect on the cardiovascular system. On the other hand, fluctuation of thyroid hormones within the normal range has been associated with long-term health risks, and might have an impact on the vasculature. This study assessed the effect of thyroid hormones on surrogate markers of arterial structure and function in a sample of euthyroid postmenopausal women.

**Methods**

This cross-sectional study recruited 106 healthy postmenopausal women with thyroid stimulating hormone (TSH) levels within the laboratory reference range (0.4–4.5 μIU/ml). Blood samples were obtained for biochemical evaluation. Anthropometric measures and blood pressure were determined in each individual. Surrogate markers of vascular structure and function were assessed by intima-media thickness as well as pulse wave velocity (PWV), augmentation index and flow-mediated dilation, respectively. The associations between arterial markers and serum TSH, free thyroxin, free triiodothyronine, as well as serum thyroglobulin and thyroid peroxidase autoantibodies, as well as serum thyroglobulin and thyroid peroxidase autoantibodies.

**Results**

A significant positive association was observed between mean measures of PWV and TSH levels in quartiles (Z coefficient value for linear trend 0.014). Significantly higher values of PWV were observed in subjects with serum TSH > 2.5 μIU/ml when compared with subjects with TSH levels < 2.5 μIU/ml (P value = 0.030, univariate). In multivariate analysis, PWV was predicted by age, insulin resistance and TSH > 2.5 μIU/ml (P, β-coefficient = 0.222; P value = 0.014). No associations were found between the remaining markers and levels of thyroid hormones, whereas thyroid antibodies were not associated with any of the arterial markers.

**Conclusion**

We demonstrated that serum TSH is an important predictor of arterial stiffness in euthyroid postmenopausal women. Women with TSH levels in the upper normal range have increased arterial stiffness compared to women with lower TSH. The upper limit of normal TSH in postmenopausal women may need reevaluation with respect to the effects on the vasculature.

**DOI:** 10.1530/endoabs.32.P187

---

*Endocrine Abstracts (2013) Vol 32*
P188
A potential predict value of circulating osteoprotegerin in diabetic patients with asymptomatic coronary artery disease
Alexander Berezn & Alexander Kremer
State Medical University, Zaporozhye, Ukraine.

Background
Osteoprotegerin (OPG) is a bone-related glycopeptide produced by vascular smooth muscle cells due to arterial damage. OPG is considered as an independent predictor of cardiovascular disease in diabetic populations. The aim of this study was to evaluate the interrelation between circulating OPG and coronary vasculature damage in type 2 diabetes mellitus patients.

Methods
One hundred and twenty six subjects with stable diabetes mellitus 2 type with previously angiographically documented asymptomatic CAD were enrolled to the study. Vessel-wall and plaque geometrical and compositional parameters were measured on contrast-enhanced CT angiography. The volume of intramural calcium of > 320 HU in major coronary vessels was measured in 428 coronary segments with a highly standardized method. Coronary artery calcification was quantified by calculating the Agatston' score index and calcification mass measurement. OPG plasma levels were measured with ELISA.

Results
Circulating OPG level was increase in 105 patients (5201 pg/ml; 95% CI = 3605–6280 pg/ml) and was normal in 21 subjects (880 pg/ml; 95% CI = 745–1140 pg/ml; P < 0.0001). The relationship between coronary artery calcium by Agatston’ score index and percent atheroma volume (PAV) was determined by linear regression. PAV and remodeling index were significantly higher in patients with elevation of OPG plasma level when compared with those who have normal OPG (adjusted odds ratio (OR) = 4.60 (95% CI = 2.23–14.50); P = 0.006). There was significant correlation between Agatston’ score index and PAV (r² = 0.46, P = 0.008). Results did not change after adjustment for age, BMI, hypercholesterolemia, arterial hypertension, and exposure of antidiabetic drugs (β = 0.490, 95% CI = 0.31–1.02, P = 0.282). Comparable results were found for calcification mass. However, minimal luminal diameter and minimal luminal area were higher in patients with normal OPG plasma level (P = 0.002).

In conclusion, we demonstrated that OPG plasma level can associate with vessel-wall thickening, percent atheroma volume, and Agatston’ score index value in type 2 diabetes mellitus patients with previously angiographically documented CAD. Results from this study underline the importance of this biomarker use for screening procedure in diabetic populations aimed to specify of coronary vasculature damage severity and probably to recalculate cardiovascular risk.

DOI: 10.1530/endoabs.32.P188

P189
Metabolic profile of transsexual persons on cross-sex hormonal therapy in a multi-center prospective intervention study
Eva Van Caenegem1,2, &, Katrien Wierckx1,2, &, Youri Taes1, & Jean-Marc Kaufman1, 3, Thomas Schreiner4,5 & Guy T Sjøen1,2

1Department of Endocrinology, Ghent University Hospital, Ghent, Belgium; 2Department of Endocrinology, Rikshospitalet, University of Oslo, Oslo, Norway; 3Center for Sexology and Gender Problems, Ghent University Hospital, Ghent, Belgium; 4European Network for the Investigation of Gender Incongruence, ENIGI, Endocrine Part, Ghent, Belgium.

Introduction
Gender differences in insulin resistance, body composition and lipid profile are well known and related to sex steroid hormones. In this study, we examine the metabolic profile of transsexual persons undergoing drastic sex steroid changes, during the first year of hormonal therapy.

Design
This research is part of a prospective intervention study conducted in several European gender teams (Ghent, Oslo, Amsterdam, and Florence).

Subjects
We present the data of Ghent gender team with 56 male-to-female (transwomen) and 24 female-to-male (transmen) transsexual persons, of whom 36 and 13 respectively have been in follow-up for 1 year of cross-sex hormonal therapy (CSH).

Methods
Standardized treatment regimens were used with oestradiolvalerate, 4 mg daily (or transdermal 100 µg/3 days for patients older than 45 years old) combined with cyproterone acetate 50 mg daily for transwomen and testosterone undecanoate i.m. 1000 mg/12 weeks for transmen. A glucose tolerance test was performed, HOMA-IR was calculated, waist:hip-ratio, lipids, total body fat and lean mass (dual X-ray absorptiometry), regional muscle mass and subcutaneous fat mass at the forearm and calf (peripheral quantitative CT-scan) and grip strength (hand dynamometer) were measured, before and after 1 year CSH.

Results
In transwomen, anti-androgens and oestrogens induced a higher total and subcutaneous fat mass and lower lean mass, muscle mass and strength and a lower waist-hip ratio (all P < 0.001). Fasting insulin and HOMA-IR were higher after 1 year of CSH. HDL, LDL, and triglycerides decreased after 1 year (all P ≤ 0.04). Transmen gained lean body mass and muscle mass and strength and lost total body fat (all P < 0.001) as well as subcutaneous fat after 1 year of testosterone (P = 0.019). A decrease in HDL and increase in triglycerides was observed (P ≤ 0.015).

Conclusions
Oestrogen and anti-androgens in transwomen lead to more fat mass with a gynoid pattern of distribution. Testosterone treatment induces a less favourable lipid profile in transmen.

DOI: 10.1530/endoabs.32.P189

P190
Changes in lipid profile and markers of metabolic syndrome after 3 years of testosterone-therapy in female-to-male transsexuals
Antonio Becerra1,2, Miriam Menacho1, Gilberto Perez-Lopez1, Rosa Villar4, Jose Manuel Del Rey1, Nuria Asenjo1, Maria Jesus Lucio1, Jose Miguel Rodriguez-Molina1 & Jose Luis Llopis3

1Hospital Universitario Ramon y Cajal, Madrid, Spain; 2Universidad de Alcala, Madrid, Spain; 3Hospital Comarcal de Melilla, Melilla, Spain; 4Hospital Universitario de Fuenlabrada, Fuenlabrada, Spain; 5Universidad Autonoma, Madrid, Spain.

Introduction
Different studies have published that testosterone therapy in men and women results in decreased HDL cholesterol and increased LDL cholesterol, and therefore an increased cardiovascular risk.

Aims
To determine whether testosterone therapy has this effect on lipid parameters and markers of metabolic syndrome (MetSyn) in female-to-male transsexuals (FMT).

Material and methods
We studied 50 FMT, aged 27.8 ± 7.6 years, at baseline and after 3 years of treatment with testosterone undecanoate (1000 mg/12 weeks, i.m.). None had done gonadectomy. Weight (W), BMI, waist and hip circumference, and systolic and diastolic blood pressure were determined. We also measured plasma levels of glucose, total cholesterol (TC), LDL, HDL, tryglicerides, apolipoprotein A-I (ApoA-I), apolipoprotein B (ApoB), lipoprotein (a) (Lp(a)), homeosticine (Hcy), 25-hydroxy vitamin D3, iron, ferritin, transferrin, total testosterone, estradiol, prolactin, sex hormone-binding globulin, delta 4-androstenedione, dehydroepiandrosterone sulphate, FSH and LH.

Results
After 3-year testosterone-therapy, there was a significant increase in the levels of testosterone (52 ± 26–697 ± 277 mg/dl, P = 0.001), TC (166 ± 29–180 ± 33 mg/dl, P = 0.031), LDL (97 ± 27–113 ± 27 mg/dl, P = 0.027), ApoB (79 ± 20–86 ± 20 mg/dl, P = 0.021), iron (74 ± 38–96 ± 47 mg/dl, P = 0.031), ferritin (44 ± 25–57 ± 32 mg/dl, P = 0.031), and Hcy (10 ± 4–12 ± 3 mg/dl, P = 0.012); and a significant decrease of HDL (53 ± 12–47 ± 11 mg/dl, P = 0.002), ApoA-I (152 ± 25–135 ± 23 mg/dl, P = 0.001), and Lp(a) (24 ± 20–18 ± 20 mg/dl, P = 0.041). The other values unchanged significantly.

Conclusion
We conclude that long-term testosterone-therapy in FMT can promote an increased atherogenic by lowering HDL and ApoA-I, and by increasing TC, ApoB, Hcy, iron, and ferritin levels. But on the other hand, it produces a decrease in Lp(a) and without changing other markers of MetSyn.

DOI: 10.1530/endoabs.32.P190
P191

Pentraxin-3 as a more sensitive marker of coronary artery disease severity than C-reactive protein

Janusz Szkodzinski1, Bartosz Hudzik1, Aleksander Danikiewicz2, Anna Pietka-Rycka1, Andrzej Lekston1 & Barbara Zabielewicz-Szkodzinska1

13rd Department of Cardiology, Silesian Center for Heart Disease, Zabrze, Poland; 2Division of Endocrinology, Medical University of Silesia, Bytom, Poland.

Introduction

Pentraxin-3 (PTX3) is an acute-phase reactant that shares structural and functional homology with C-reactive protein (CRP). However, unlike CRP, which is synthesized mainly in the liver, PTX3 is produced at the site of inflammation. It has been suggested that PTX3 plays the same role in the periphery that CRP does in circulation. PTX3 may represent a rapid marker for local inflammation.

Methods

Fifty three patients with stable coronary artery disease (CAD) were enrolled. Coronary angiography was performed during index hospitalization because of the clinical presentation. Blood samples were collected on admission. Plasma concentration of PTX3 and high-sensitivity CRP (hsCRP) were determined.

Results

Median PTX3 concentration was 0.92 μmol/l (0.58–1.40). Median hsCRP concentration was 0.90 mg/l (0.75–1.10). There was a positive correlation between PTX3 and total cholesterol (R=0.34; P=0.01), PTX3 and LDL cholesterol (R=0.35; P=0.005), and PTX3 and hsCRP (R=0.46; P=0.0005). We found no correlation between hsCRP and all laboratory parameters. We found higher PTX3 concentrations in patients with Canadian Cardiovascular Society (CCS) functional class 2 (compared to CCS functional class 3), in patients with multi-vessel CAD (compared to single-vessel CAD), and in patients taking nitrates. Lower PTX3 concentrations were reported in patients taking calcium channel blockers (amlodipine), hsCRP concentrations remained similar among these subgroups of patients. Conclusions: PTX3 was a marker of clinically more advanced CAD (CCS2 vs CCS3; nitrates vs no nitrates) and of a more severe atherosclerosis (single-vessel CAD vs multi-vessel CAD). PTX3 is also associated with other cardiovascular risk markers (total cholesterol, LDL cholesterol, and hsCRP). PTX3 may be a potential early marker of cardiovascular risk before the increase of systemic markers like hsCRP.

DOI: 10.1530/endoabs.32.P191

P192

Effect of cross-sex hormone treatment on lipid profile in transsexual individuals: experience in a specialized unit in Catalonia

Carmen Quirós López, Ioana Patrasciou, Mireia Mora Porta, Gloria Beatriz, Aranda Velázquez, Felicia Hanzu, Esther Gómez Gil, Teresa Gódás Sieso & Irene Halperin Robinovich

Hospital Clínic Universitari, Barcelona, Spain.

Objectives

To assess baseline differences on lipid profile in individuals with gender identity disorder (male to female, M2F and female to male, F2M) in relation to prior cross-sex hormone treatment (CHT) or not, and changes in the lipid profile after 24 months of treatment and follow-up in our unit.

Methods

Transversal study by revision of medical records of 235 patients visited for first time in our service from 2006 to 2010. Clinical and analytical revision was made on the first visit, 6, 12, and 24 months.

Results

At baseline, F2M (92 patients, 39%) transsexuals were younger than M2F (143 patients, 61%) (27.9 vs 32.5 years; P=0.001). In M2F patients, 61% (27/9; 8.7 vs 52.0 vs 9.8 years; P=0.05) had lower triglycerides levels (68.8±29.7 vs 92.2±7.14 mg/dl; P=0.0001) and higher HDL levels (51.4±12.3 vs 45.0±11.7 mg/dl; P=0.0001). No differences in baseline lipid profile was observed between individuals with previous hormonal treatment versus naive in none of the two groups, but in M2F group, individuals with previous treatment had a higher weight (71.8±12.3 vs 67.0±12.1; P=0.038).

In F2M transsexuals group, at 24 months follow-up, we observed a significant increase in weight (71.1±13.0 vs 73.8±5.2 kg; P=0.0001) and BMI (25.3±5.5 vs 24.5±5.3 kg/m²; P=0.0001) without significant changes in the lipid profile. On the other hand, at 24 months follow-up, in the F2M transsexuals group, we observed a significant increase in weight (67.2±13.6 vs 69.8±12.5 kg; P=0.005) and BMI (25.3±5.0 vs 26.4±4.1 kg/m²; P=0.0002) and a worsening of lipid profile with increased total cholesterol (168.5±35.8 vs 178.2±37.9 mg/dl; P=0.003), triglycerides (71.7±31.4 vs 105.3±70.2 mg/dl; P<0.005), LDL (106.0±27.9 vs 115.2±29.1 mg/dl; P=0.018), no-HDL cholesterol (118.7±32.5 vs 136.3±34.1; P<0.000) and decrease in HDL (52.8±13.5 vs 45.4±14.5 mg/dl; P=0.0001).

Conclusions

CHT leads to changes in lipid profile at 24 months, highlighting the worsening in F2M transsexuals.

DOI: 10.1530/endoabs.32.P192

P193

HDL cholesterol subfractions and the effect of testosterone replacement in hypogonadism

Erol Bulu1, Alper Sonmez2, Serkan Tapam2, Abdullah Taspinar1, Aydogan Aydogdu1, Coskun Meric1, Yalcin Basaran1, Gokhan Uckaya1, Muhittin A Serdar2, Ismail Kurt2 & Omer Azal1

1Department of Endocrinology and Metabolism, Gulhane Military Medical Academy, Ankara, Turkey; 2Department of Clinical Biochemistry, Gulhane Military Medical Academy, Ankara, Turkey.

Objective

To assess baseline differences on lipid profile in individuals with hypogonadism.

Methods

We designed a prospective study to investigate the HDL subfractions in treatment naïve subjects with hypogonadism and the effects of two different testosterone replacement regimens on the HDL subfractions.

Results

Young male patients with congenital hypogonadotropic hypogonadism (CHH) and 70 age and BMI-matched healthy males were enrolled in the present study. The patients were assigned to receive intramuscular injections of testosterone esters 250 mg every 3 weeks and transdermal testosterone applications 50 mg daily. Biochemical investigations including HDL subfractions and insulin resistance were done. Patients with CHH had higher levels of insulin, HOMA-IR, WC, triglyceride, and diastolic blood pressure. Although, the HDL cholesterol concentrations were similar in both groups, hypogonadal patients had lower HDL2 and higher HDL3 levels. The total testosterone levels were independent determinants of the HDL2 subfractions. During the follow-up, a significant increase in the BMI and WC values and a significant decrease in the levels of total cholesterol, HDL cholesterol and HDL3 were observed. No difference was present between the two treatment arms. These results show that low testosterone levels in hypogonadism may be associated with unfavorable HDL subfractions. Nevertheless, neither metabolic disorders nor the unfavorable HDL subfractions were able to improve with testosterone replacement therapy. The implications of these findings for the cardiovascular health should be sought with prospective follow up studies.

DOI: 10.1530/endoabs.32.P193

P194

The activity of inflammation and the blood redox status in patients with coronary heart disease and type 2 diabetes mellitus

Inna Buko1, Tatiana Mochkort2, Helena Konstantinova1, Natalia Tsapeva1,2 & Andrey Moiseenok3

1Republican Scientific-Practical Center “Cardiology”, Minsk, Belarus; 2Belarusian State Medical University, Minsk, Belarus; 3Scientific-Practical Center for Foodstuffs National Academy of Sciences of Belarus, Minsk, Belarus.

Objective

To determine the relationship between indicators of inflammation and the blood redox status of type 2 diabetic (T2DM) patients with and without coronary heart disease (CHD).

Methods

Forty patients with T2DM and CHD (group 1), 67 patients with T2DM without cardiovascular complications (group 2), 98 healthy subjects (group 3) were included in this study. Serum concentrations of IL6 and IL8 were determined by ELISA using commercial kits. Concentrations of thiobarbituric acid reactive substances (TBARS) both in plasma and in atherogenic lipoprotein, total glutathione (GSH) and oxidized glutathione, as well as the activity of glutathione peroxidase and glutathione reductase in erythrocytes, and that of catalase in plasma were determined by spectrophotometric methods. The glutathione redox potential (ER), was calculated by the Nernst equation.
The increased in IL6 concentration was found in group 1 (87%, \( P=0.000 \)) and group 2 (20%, \( P=0.007 \)) compared to group 3. The IL8 concentration was increased only in group 1 (56%). Decreased activity of catalase and glutathione peroxidase was revealed in groups 1 and 2 compared to group 3. While the decrease in GSH and GSH concentrations was found only in group of patients with T2DM and CHD (58 and 71%, respectively). This group of patients was characterized by the increased values of \( E_{90} \) (36.3 mV, \( P=0.000 \)) compared to the healthy subjects. Consequently, patients with T2DM and CHD are different from diabetic patients without cardiovascular complications to have increased pro-inflammatory cytokine IL6, decreased antioxidant capacity of the erythrocytes glutathione system and increased \( E_{90} \) values. High cytokine concentrations and changes in glutathione level as well as \( E_{90} \) can be considered as prognostic markers for assessing the risk of CHD progression in diabetic patients.

**Utility of N-terminal pro-brain natriuretic peptide in the evaluation of patients with high clinical probability of non-ST segment elevation acute coronary syndrome**

Alina Mihaela Pasică1,2, Mariana Radol1,2, Alina Bisoc1,2 & Marius Alexandru Moga1,2

1Transilvania University of Brasov, Brasov, Romania; 2Faculty of Medicine, Brasov, Romania.

**Introduction**

The study aimed to analyze the efficiency of a concomitant N-terminal pro-brain natriuretic peptide (NT-proBNP) and cardiac high-sensitivity troponin T (hs-cTnT) testing in diagnosing non-ST-segment-elevation myocardial infarction (NSTEMI) in patients initially negative for the standard fourth-generation assay of cardiac troponin T (cTnT), but with high clinical probability of non-ST-segment-elevation acute coronary syndrome (NSTEMI-ACS).

**Methods**

One hundred and eight patients, 57 (52.8%) men, mean age 61.3 ± 15.4, admitted for high-risk symptoms of NSTEMI-ACS in a time-interval <4 h after the symptoms onset, but with initial cTnT levels <0.01 ng/ml, were prospectively investigated. Plasma cTnT, NT-proBNP, and hs-cTnT were measured by electrochemiluminescence on admission, then 3 and 6 h afterwards. NSTEMI was considered at plasma hs-cTnT levels ≥ the 99th percentile cut-off (0.014 ng/ml), and ≥ 20% dynamic variation within 6 h. Aortic dissection, pulmonary embolism, left ventricular hypertrophy, myocarditis, renal dysfunc-

**Results**

Using a combination of hs-cTnT plasma levels ≥0.014 ng/ml and a ≥ 20% 6-h hs-cTnT dynamic plasmaic variation testing, NSTEMI was diagnosed within the cTnT "blind interval" in 37 (34.26%) additional patients with high-risk symptoms of NSTEMI-ACS. The ari under the receiver operating characteristic (AUC) for NT-proBNP in diagnosing NSTEMI was 0.68 (95% CI: 0.56-0.74, \( P=0.0345 \)).

**Conclusion**

A multimarker strategy using NT-proBNP concomitant with hs-cTnT testing on admission in the early diagnosis of NSTEMI in patients with high clinical probability of acute coronary syndrome showed only an additional value of NT-proBNP testing.

**Impact of subclinical thyroid dysfunction on mortality among patients presenting with cardiovascular events**

Paulette Nacip, Ma Luisa Arkoncel, Gregory Joseph Ryan Ardeia & Cecilia Jimeno

Philippine General Hospital, University of the Philippines, Manila, The Philippines.

**Introduction**

The possible clinical impact of subclinical thyroid dysfunction on patients with cardiovascular events is important if one considers the high incidence of a mildly altered thyroid hormone pattern in this population. This study aims to determine the prevalence of subclinical thyroid dysfunction among patients presenting with cardiovascular events in Philippine General Hospital, and its impact on mortality.

**Methodology**

A cross sectional, prospective cohort study, involving 163 adult patients with cardiovascular events. Pregnant, and all patients who have clinically apparent thyroid disease or taking thyroid medications, or any other medications that may affect thyroid function testing were excluded. Patients were grouped as having overt thyrotoxicosis, subclinical hyperthyroidism, euthyroidism, overt hypothy-

**Results**

Patients with subclinical hyperthyroidism were older (66.9 vs 56.9 years, \( P=0.0020 \)), and more were diabetic (55.6 vs 23.6, \( P=0.039 \)), while those with subclinical hypothyroidism and nonthyroidal illness have a higher need for mechanical ventilation (33.3 vs 9%, \( P=0.022 \); 25.7 vs 9%, \( P=0.015 \) respectively), compared to euthyroid. Prevalence of subclinical thyroid dysfunction was 32.5%. Of these, 5.5% had subclinical hypothyroidism, 5.5% had subclinical hyperthyroidism, and 21.5% had nonthyroidal illness. Higher incidence of acute coronary event and heart failure among patients with subclinical thyroid dysfunction (\( P=0.031 \)) was noted. The overall death rate was also higher (17.3 vs 9.2%).

**Conclusion**

In patients with cardiovascular events, the prevalence of subclinical thyroid dysfunction was 32.5%. Higher incidence of acute coronary event and heart failure was observed in the population. Subclinical hyperthyroidism was
significantly associated with older age and diabetes, while subclinical hypothyroidism and nonthyroidal illness with need for mechanical ventilation.

DOI: 10.1530/endoabs.32.P197

**P198**

Abstract withdrawn.

DOI: 10.1530/endoabs.32.P198

**P199**

Lipid levels in patients with rheumatoid arthritis and the effect of rituximab

Ilfigenia Kostoglou-Athanassiou1, Eleni Xanthakou2, Alkaterini Tzanavari3, Anastasios Gkountouvas1, Nicolasos Dadiras1, Eirini Koutsika1 & Panagiotis Athanassiou3

1Department of Endocrinology, Red Cross Hospital, Athens, Greece; 2Endocrinologist, Athens, Greece; 3Department of Rheumatology, St Paul’s Hospital, Thessaloniki, Greece.

Rheumatoid arthritis (RA) is known to be associated with cardiovascular comorbidity. In particular, patients with RA are known to be at increased for the development of atherosclerosis. Treatment with biological agents in RA may affect lipid levels.

**Aim**

The aim was to study the effect of rituximab treatment on lipid levels in RA patients.

**Methods**

In a cohort of 20 patients with RA lipid levels were studied before, 6 and 12 months after treatment with the biological agent rituximab (2 × 1000 mg i.v. infusions 2 weeks apart) at baseline, 6 and 12 months later. All patients fulfilled the 2010 ACR/EULAR criteria for RA. Total cholesterol, HDL, LDL cholesterol, and triglyceride levels were measured at baseline, 6 and 12 months later.

**Results**

At baseline total cholesterol was 207.41±8.33 mg/dl (mean±s.e.m.), 6 and 12 months later increasing to 218.27±7.02 and 226.12±8.71 mg/dl respectively (P<0.001, Student’s t-test). At baseline HDL cholesterol was 59.17±3.31 mg/dl, 6 and 12 months later increasing to 66.05±3.49 and 58.81±3.04 mg/dl, respectively (P<0.001). At baseline LDL cholesterol was 122.92±8.96 mg/dl, 6 and 12 months later increasing to 124.58±5.61 and 141.56±7.95 mg/dl respectively (P<0.001). At baseline triglyceride levels were 138.50±13.91 mg/dl, 6 and 12 months later decreasing to 122.55±10.52 and 118.65±9.91 mg/dl respectively (P<0.001).

**Conclusion**

Treatment with the biological agent rituximab in RA resulted in an increase in total cholesterol, paralleled by an increase in HDL cholesterol, LDL cholesterol, while triglyceride levels decreased. The adverse effect on total cholesterol levels may be counteracted by the parallel increase in HDL thus conferring a beneficial effect on the patients as far as cardiovascular risk is concerned. These findings have therapeutic implications as the effect of rituximab on lipid levels may render systematic treatment with statins necessary in rheumatoid arthritis.

DOI: 10.1530/endoabs.32.P199

**P200**

Linear growth and IGF1 concentrations in children cyanotic and acyanotic congenital heart disease before vs after intervention

Ashraf Soliman1, Khaled Elilithy1, Ayman Khella1, Haytham Yassin1, Emad Shatla1, Amil Sab1 & Rania Elalaily3

1Hamad Medical Center, Doha, Qatar; 2Primary Health Care, Doha, Qatar.

**Objectives**

To measure linear growth of patients and the magnitude of catch-up growth and changes in IGF1 concentration.

**Design**

This prospective study recorded the anthropometric data and measured the IGF1 of 32 infants and children with congenital acyanotic heart disease (CAHD) with left to right shunt (14 VSD, 10 ASD, and 8 PDA) without heart failure, and 15 with cyanotic heart disease (CCHD) before (B) and a year after (A) surgical or catheter intervention.

**Results**

At presentation patients with CHD height SDS (HSDDS) and GVSDS were significantly decreased vs normal controls. The BMI of CCHD were significantly lower than normal controls. Before intervention, CCHD had significantly decreased length SDS (LSDS) and growth velocity SDS (GVSIDS) vs CAHD. One year after intervention the HSDDS, GVSIDS increased significantly in patients with CCHD and CAHD. After intervention CCHD had higher GVSIDS compared to children with CAHD. BMI increased significantly in patients with CCHD after intervention. IGF1 levels increased significantly in both groups of patients after intervention. The HSIDS after treatment was correlated with the IGF1 concentration (r=0.70, P<0.001). In CAHD the shunt size was correlated negatively with BMI before intervention (r=0.39, P<0.01). GVSIDS after intervention surgery was correlated with age at operation (r=−0.62, P<0.001) and BMI after intervention (r=0.57, P<0.001).

**Table 1**

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>CCHD-</th>
<th>CCHD-</th>
<th>CAHD-</th>
<th>CAHD-</th>
<th>Controls-</th>
<th>Controls-</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B=15</td>
<td>A=15</td>
<td>B=32</td>
<td>A=32</td>
<td>B=50</td>
<td>A=50</td>
</tr>
<tr>
<td>Age mon</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11.9</td>
<td>24.6</td>
<td>30</td>
<td>43.2</td>
<td>18.5</td>
<td>32.4</td>
</tr>
<tr>
<td>LSDS</td>
<td>−2.6</td>
<td>−1</td>
<td>−1.1</td>
<td>−0.55</td>
<td>−0.2</td>
<td>−0.1</td>
</tr>
<tr>
<td>GVSIDS</td>
<td>−1.3</td>
<td>3.5</td>
<td>−0.7</td>
<td>2.5</td>
<td>0.31</td>
<td>0.25</td>
</tr>
<tr>
<td>BMI</td>
<td>14.5</td>
<td>16.4</td>
<td>15</td>
<td>15.7</td>
<td>16.3</td>
<td>16.7</td>
</tr>
<tr>
<td>IGF1 (ng/ml)</td>
<td>41.5</td>
<td>72.3</td>
<td>53</td>
<td>79</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

**Conclusions**

These data denoted that early surgical interference and good weight gain have beneficial effect on postoperative growth spurt.

DOI: 10.1530/endoabs.32.P200

**P201**

Changes of expression of regulators of calcification in different stages of atherosclerosis in vasculature and bone

Natascha Schweighöfer1, Ariane Angeleitner2, Martina Graf-Rechberger2, Nicole Hacker1, Martin Schweiger1, Olivia Trummer1, Thomas Pieber1, Matthias Ulbing1, Helmut Müller1 & Barbara Obermayer-Pietsch1

1Department of Internal Medicine, Division of Endocrinology and Metabolism, Medical University of Graz, Graz, Austria; 2Institute of Pathology, Medical University of Graz, Graz, Austria.

Calcification is physiologically present in bone but also pathophysiologically in the vasculature, favouring cardiovascular diseases. Our aim was to investigate changes in the expression of calcification regulators (CR) during vascular calcification in bone and vasculature. Gene expression levels of OPG, RANKL, OPN, MGP, BSP-II and RUNX2 were determined in bone, aorta and arteria ilica externa tissue samples of 22 transplant donors. Gene expression levels during atherosclerotic changes in the vessels were investigated using three histological stages of atherosclerosis (0) no changes, (1) intima thickening or (2) intima calcification. Patients’ other tissue samples were subgrouped accordingly. In addition, serum measurements of PTH, Fetuin A, 25(OH)2-Vitamin-D3 and 1,25(OH)2-Vitamin-D3 were performed.

**Results**

The comparison of gene expression of CR in vascular tissue revealed that the expression of CR was already changed in thickened vessels and kept stable during calcification. Therefore, we compared unaffected with affected vessels. We demonstrated that the expression of BSP-II and OPN were significantly (P=0.034) and RANKL expression was by trend decreased (P=0.085) in affected vessels compared to unaffected ones. In comparing bone and vascular tissue, patients with no atherosclerosis (stage 0) showed no differences in CR expression in bone and vascular tissue. In stage 1 patients, expression of MGP (P=0.002) and OPG (P=0.001) was significantly higher in bone than in both vessel types, whereas in stage 2 patients, OPG expression increased in both vessel types. Serum levels of Fetuin A were significantly lower in stage 2 patients compared to the other stages (P=0.007).

Endocrine Abstracts (2013) Vol 32
Conclusion
Our study indicates that changes in the expression of CR in the vessel wall as well as in bone tissue occurs already in the stage of thickening of the vessel wall, even prior to deposition of calcium/phosphate precipitation.

DOI: 10.1530/endoabs.32.P201

P202
Dyslipidemia associated with m-TOR inhibitors treatment
Joana Couto, Raquel Martins, Filipa Carneiro, Ana Paula Santos & Isabel Torres
Portuguese Institute of Oncology FG, Porto, Portugal.

Introduction
Therapeutic approach of patients (pts) with metastatic renal cell carcinoma (mRCC) may include the use of biological agents such as m-TOR inhibitors: temsirolimus (TM) and everolimus (EV). Its use is associated with metabolic dysfunction, especially with everolimus: hyperglycemia (37% TM treated pts vs 72% EV treated pts), hypercholesterolemia (25% TM treated pts vs 81% EV treated pts) and hypertriglyceridemia (30% TM treated pts vs 73% EV treated pts). Discontinuation of therapy is suggested, if grade 4 toxicity is observed: blood glucose >500 mg/dl, total cholesterol (TC) >500 mg/dl and triglycerides (TG) >10×UNL.

Objective and methods
Retrospective evaluation of lipid profile (LP) in pts with mRCC treated at our institution with m-TOR inhibitors (TM and EV), between June 2010 and August 2012. We evaluated TC and TG levels. Pts with hypothyroidism (previous treatment with sumitib) and pts without baseline LP were excluded.

Results
We evaluated five pts, 4f, 1m, aged between 55 and 70 years. Three patients were treated with TM and two with EV. All patients had dyslipidemia at baseline. Average TC and TG values were assessed before treatment: CT 224 ± 54 mg/dl (191 mg/dl – TM group vs 275 mg/dl – EV group); TG 247 ± 115 mg/dl (202 mg/dl-TM group vs 313 mg/dl-EV group). After therapy (med. 2.4 months): EV, CT 156 ± 54 mg/dl (115 mg/dl - lower), TG 170 ± 54 mg/dl (lower vs TM). TC’s increase in the group of pts treated with TM and EV was +25% (with TM) vs +23% (with EV), and TG’s increase was +101% (with TM) vs +150% (with EV).

Conclusions
Therapy with m-TOR inhibitors in this small number of pts was associated with an increase in the lipid parameters assessed, especially TG. Metabolic toxicity in patients on TM and EV should be promptly addressed and requires an intervention between health professionals in order to develop evaluation and follow-up protocols.

DOI: 10.1530/endoabs.32.P202

P203
Rising prevalence of fatty liver in India and its correlates
Jayashree Gopal & R Usha
Apollo Hospitals, Chennai, India.

Among individuals who came for master health check up to Apollo hospitals, Chennai between June 2011 to November 2011, 750 patients were recruited based on the inclusion and exclusion criteria. Those who showed fatty liver on ultrasonography were compared with those who had normal liver parenchyma. People with acute medical illness, known hepatic disease, known renal disease, people who consume excessive alcohol (> 20 g/day), patients on medications that cause hepatotoxicity (such as estrogens, corticosteroids, amiodarone, valproate; at present or within the last 2 years) were excluded.

Our study showed 44% prevalence of fatty liver, which is much higher than those reported in last decade and certainly indicates an upward trend in increasing prevalence of FLD (earlier studies have shown prevalence ranging from 10 to 22%). In this study FLD was present mainly in the middle-aged group with peak occurrence around 40–50 years with mean age at presentation being 47 ± 11 years. Of them FLD was more common in men and this might be due to higher waist–hip ratio in men as compared to women, which is an indicator of central obesity and insulin resistance. We also found that fatty liver was undoubtedly associated with high BMI, increased waist circumference and WHR. Eight percent of the patients with FLD were either overweight or obese (49 and 31% respectively). As increased ALT has been reported to be positively associated with FLD, we also found that 30% of patients with FLD had elevated AST (>35 U/l) and ALT (>45 U/l) with the mean ALT greater than AST (44±3.2 vs 34±4.0). Seventy-two percent had ALT: AST ratio greater than the reverse ratio in FLD group (22%). Also, 76% of FLD group were either diabetic (36%) or pre-diabetic (40%) with only 24% being normal. The mean fasting and 2 h postprandial blood sugar levels in FLD patients were markedly higher than the control group (122±45 and 167±83 respectively). In this study, though the occurrence of hypertension was not significant, there was significant increase in the mean systolic BP in FLD patients (130.37±16.59). Seventy-three percent of our patients with FLD had metabolic syndrome. This is higher than that reported in a study conducted in South India. When compared to the last decade, the overall prevalence of FLD is progressively increasing in India in parallel with the increasing prevalence of T2DM, obesity and metabolic syndrome.

DOI: 10.1530/endoabs.32.P203

P204
CNRI polymorphisms and metabolic disorders in woman with PCOS - preliminary report
Andrzej Milewicz1, Łukasz Łaczmąsk1, Agnieszka Lenarcik1, Justyna Kulikowicz1, Anna Trzmiel-Bira1, Barbara Stachowska1, Diana Jędreyjak1, Ewa Sadowska1, Katarzyna Kolacko1, Mauryca Pawlak1, Anna Arkowska1, Urszula Dobroń1, Lidia Hirme2 & Felicie Lwow3
1Department of Endocrinology, Diabetology and Isotope Therapy, Wroclaw Medical University, Wroclaw, Poland; 2Department of Radiology, Wroclaw Medical University, Wroclaw, Poland; 3Department of Gynecology, Wroclaw Medical University, Wroclaw, Poland; 4Department of Health Promotion, Faculty of Physiotherapy, University School of Physical Education, Wroclaw, Poland.

The endocannabinoid system has been suspected to contribute to the association of visceral fat accumulation with metabolic diseases. Insulin resistance play important role in etiology in PCOS. The aim of our study was developed the role of CNRI polymorphisms (rs806368, rs12720071, rs1049353, 806381, rs10485170, rs6454674, rs203239) in metabolic disorders in woman with PCOS. 88 woman (20–35 years old) with PCOS (recognized using Rotterdam criteria) and 77 woman (20–35 years old) as homogenous controls group were study. Lipids profile and carbohydrate metabolisms in serum using standard methods were study. Genomic DNA were isolated using standard method. To amplify the genetic material of the PCR technique was used. To polymorphisms identification minisequencing was used. Reaction products were separated on Genetic Analyser ABI 3100. For statistic analysis ANOVA test was used. In polymorphism rs12720071 eight woman with PCOS present genotype G/G in contrast to control we can't find such a genotype. These genotype in contrast to control can't find such a genotype. These genotype in polymorphism rs1049353 in PCOS group present a higher WHR vs other genotype in contrast to control group. Also other polymorphism rs10485170 in genotype A/G show significantly lower LDL cholesterol levels in controls but not in woman with PCOS. In polymorphism rs203239 genotype C/C was connected with elevated levels of free androgens index in PCOS patients.

Our preliminary results can suggest the potential role of CNRI polymorphisms PCOS etiology what need further study.

DOI: 10.1530/endoabs.32.P204

P205
Oleic vs linoleic effects on hepatic sex hormone-binding globulin production
Christina Saez Lopez, Cristina Hernandez, Rafael Simo & David M Selva
Research Institute Vall d’Hebron, Barcelona, Spain.

Low plasma SHBG is an independent risk factor of cardiovascular disease. Our recent work has shown that SHBG gene expression can be regulated indirectly through HNF4z gene expression. In this regard, we have identified that an
increase in hepatic palmitate induced by high carbohydrate diets and pro-inflammatory cytokines (TNFα and IL-1β) was able to reduce hepatic HNF4α protein levels which, in turn, decreased SHBG production. The Mediterranean diet, in which olive oil is the primary source of fat, is associated with a lower risk of cardiovascular disease. Since olive oil is the primary source of fat intake, the Mediterranean diet is high in monounsaturated fatty acids (MUFA), specifically oleic acid. The purpose of this study was to investigate the effects of oleic and linoleic acids in the regulation of SHBG production in HepG2 cells and to examine the underlying molecular mechanisms. We provide evidence that oleic acid treatment increased SHBG (mRNA and protein) when compared with linoleic acid treatment over the course of three days in HepG2 cell cultures. Oleic acid and linoleic acid treatment did not change HNF4α (mRNA and protein levels). However, oleic acid treatment reduced PPARγ (mRNA and protein levels), a well-recognized SHBG inhibitor, when compared with linoleic acid treatment. Finally, oleic acid treatment produced a reduction in PPARγ binding and an increase in HNF4α binding to the SHBG promoter when compared with linoleic acid treatment in CHIP assays. In conclusion, our results provide evidence that treatment with oleic acid increases SHBG production, mainly by down-regulating PPARγ. Our findings suggest that the effect of oleic acid in increasing SHBG could be a new mechanism involved in the beneficial effect of Mediterranean diet on cardiovascular disease.

DOI: 10.1530/endoabs.32.P205

P206

Post prandial responses in insulin, free fatty acid and endothelial function following to Malaysian vs Mediterranean meals among healthy subjects

Norasyikin A Wahab, Yusniiza Yusoff, Amiilyaton Mohd Razali, Suehazlyn Zainudin, Rohana Abd Ghani, Norlela Sukor, Norlaila Mustafa, Shamsul Azhar Shah, Barakatun Nisak Mohd Yusof & Nor Azmi Kamaruddin

Universiti Kebangsaan Malaysia, Bangi, Selangor, Malaysia.

Introduction

Refined carbohydrates, which constitute the staple diet in most cultures may exaggerate postprandial responses in term of insulin, free fatty acid and vascular function. These changes may contribute the onset of metabolic syndrome and diabetes among those at high risk of developing these diseases.

Objective

To determine the postprandial insulin, free fatty acids levels and endothelial function responses in healthy subjects to two different breakfast meals, Mediterranean vs Malaysian diet with different carbohydrate contents, glycemic index and glycemic load.

Methods

Twenty subjects were made to take two different meals, Mediterranean meals; low Glycaemic Index (GI) and low Glycaemic Load (GL) and Malaysian meals (high GI and high GL) a week apart. Blood parameters including fasting serum lipid, serum insulin, serum non esterified free fatty acid were taken at 0, 30, 60, 90 and 120 min after each meals. Blood glucose was also taken at baseline and 120 min postprandially.

Results

Twenty subjects were randomized to either Mediterranean meal or Malaysian meal. Baseline clinical and demographic data parameters were comparable for both meals. With both meals there was an increase in serum triglyceride with a corresponding drop in HDL and LDL levels throughout the 2-h postprandial period. There is a significant increase in the serum insulin level with Malaysian meal (P=0.002) compared to Mediterranean meal (P=0.012). However, the non esterified fatty acid levels were significantly lower in Malaysian meal (P=0.001) compared to Mediterranean meal.

Conclusion

Malaysian meal which is characterised by high GI and GL stimulated significant increase in insulin responses in the setting of significant drop in free fatty acid compared to Mediterranean meal.

Key Words

insulin; serum nonesterified fatty acid (NEFA). DOI: 10.1530/endoabs.32.P206

P207

Subclinical atherosclerosis and cardiovascular risk in healthy, young menopausal women

Eleni Armenti1, Kimon Stamatelopoulos2, Georgios Giorgiopoulos2, Evangelia Kouskouni3, Maria Creata1, Andreas Alexandrou4, Christos Papamichael2 & Irene Lamberinoudaki1

1Department of Obstetrics and Gynecology, Areteiaio Hospital, University of Athens, Athens, Attiki, Greece; 2Department of Therapeutics, Alexandra Hospital, University of Athens, Athens, Attiki, Greece; 3Biochemical Laboratory, University of Athens, Areteiaio Hospital, Athens, Attiki, Greece.

Introduction

Delayed diagnosis of a cardiovascular event is related with higher case-fatality rate in women as compared to men. In fact, accumulating evidence supports an association between the menopausal status and the development of cardiovascular disease (CVD). We aimed to assess the extent of subclinical vascular disorders in young, healthy postmenopausal women, with respect to the calculated cardiovascular risk.

Methods

This cross-sectional study recruited 120 healthy, young postmenopausal women without clinically overt CVD or diabetes, classified as not high-risk by the Heartscore. In addition to risk factors used for Heartscore calculations, we assessed menopausal age and associated metabolic risk factors (e.g. triglycerides, waist circumference, fasting blood glucose, and HOMA-IR). Carotid–femoral pulse wave velocity, carotid and femoral intima–media thickness in the abnormal range as well as atheromatous plaques both in carotid and femoral arteries were used to define the presence of subclinical atherosclerosis.

Results

Subclinical atherosclerosis was identified in up to 55% of women. In addition, presence of at least one plaque in carotid arteries was identified in up to 22.5% of women. Subjects with subclinical atherosclerosis had higher age and menopausal age, blood pressure and HOMA-IR. By multivariate analysis menopausal age and an increase in HNF4α (mRNA and protein) binding to the SHBG promoter when compared with linoleic acid treatment in CHIP assays. In conclusion, our results provide evidence that treatment with oleic acid increases SHBG production, mainly by down-regulating PPARγ. Our findings suggest that the effect of oleic acid in increasing SHBG could be a new mechanism involved in the beneficial effect of Mediterranean diet on cardiovascular disease.

DOI: 10.1530/endoabs.32.P207

Subclinical atherosclerosis in healthy, young menopausal women


1 Department of Obstetrics and Gynecology, Areteiaio Hospital, University of Athens, Athens, Attiki, Greece; 2 Department of Therapeutics, Alexandra Hospital, University of Athens, Athens, Attiki, Greece; 3 Biochemical Laboratory, University of Athens, Areteiaio Hospital, Athens, Attiki, Greece.

Introduction

This cross-sectional study recruited 120 healthy, young postmenopausal women.
P208
Comparative effects of atorvastatin and rosuvastatin on vitamin D levels, glucose metabolism and systematic inflammation in non-diabetic patients with dyslipidaemia: a prospective randomised open-label study
Panagiotis Anagnostis1, Fotini Adamidou1, Aristidis Slavakis1, Stergios Polyzos1, Athanasios Panagiotou1, Despina Selalmatzidou1, Eleni Karathanasi1, Maria Poulosouchidou1 & Marina Kita1
1Department of Endocrinology, Hippokration Hospital of Thessaloniki, Thessaloniki, Greece; 2Hormone Assay Laboratory, Department of Biochemistry, Hippokration Hospital of Thessaloniki, Thessaloniki, Greece.

Introduction
Low levels of 25-hydroxy-vitamin D [25(OH)D] have been recognized as a new cardiovascular disease risk factor. Conflicting data exist regarding the effect of statins on 25(OH)D levels and glucose metabolism.

Methods/design
This was an open-label randomized prospective comparative study evaluating the effects of atorvastatin and rosuvastatin at equivalent doses on 25(OH)D levels, glucose homeostasis and systemic inflammation in non-diabetic patients with dyslipidaemia. Fifty-two patients were randomly assigned to atorvastatin 20 mg/day (n=28, aged 56.1±2.2 years, 22 females) or rosuvastatin 10 mg/day (n=24, aged 57.4±1.9 years, 20 females). Total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), fasting plasma glucose, insulin, homeostasis model assessment-insulin resistance (HOMA-IR), glycosylated hemoglobin A1c (HbA1c) and high-sensitivity C-reactive protein (hsCRP) levels were measured at baseline and after 12 weeks. There were no differences in baseline characteristics between the two groups.

Results
Both statins significantly reduced TC, TG and LDL-C levels. The reduction in LDL-C was greater with rosuvastatin (49.4 vs 41.7%, P=0.015). The increase in 25(OH)D levels with both statins was not statistically significant (from 21.7±1.9 to 23.5±2.3 ng/ml with atorvastatin (P=0.205) and from 25.3±1.8 to 27.0±2.4 ng/ml with rosuvastatin (P=0.306)). Rosuvastatin was associated with a significant reduction in insulin levels (from 6.7±0.6 to 5.2±0.7 μIU/ml (−8.5%), P=0.048)), although not in HOMA-IR. The respective changes with atorvastatin were not significant. The effect of both statins on fasting glucose and HbA1c levels was neutral.

Regarding systematic inflammation, only atorvastatin significantly reduced hsCRP levels (from 4.1±1.4 to 3.0±0.7 mg/l (−13.5%), P=0.025).

Conclusions
Statins did not affect 25(OH)D levels in the present study. Rosuvastatin was associated with a reduction in insulin levels without affecting insulin resistance, while the effect of atorvastatin on glucose homeostasis was neutral. However, atorvastatin, led to a significant reduction in systematic inflammation compared with rosuvastatin.

DOI: 10.1530/endoabs.32.P208

P209
Clinical experience with exenatide and liraglutide in the internal medicine service two of hospitals in Valencia
Juano Jose Tamartii-Garcia1, Belen Roig-Espert1, Marta Balaguer-Catelan1, Amparo Lozano-Cebrian1, Ana Ruiz-Garcia1, Belen Vizcaino-Castillo1, Patricia Sacie-Reyes1 & Arturo Artero-Mora1
1Dr Peset University Hospital, Valencia, Spain; 2Manises Hospital, Valencia, Spain.

Background and objective
The upcoming new marketing presentations GLP1 analogues with a dosage more comfortable for patients, we wanted to revise the two we currently have on the market. The target of this study is to determine glycated hemoglobin (HbA1c) at 6 months of treatment, changes in weight, body mass index (BMI) and tolerance.

Design and methods
Observational study that included 60 patients with diabetes mellitus type 2 followed in two Internal Medicine Service. The inclusion of patients was follow in two Internal Medicine Service. The inclusion of patients was twice daily and Liraglutide 1.2 mg daily. Determinations baseline and 6 months of treatment.

Results
– Baseline data: Exenatide/Liraglutide (weight 102.61/105.73, BMI 38.19/41.35, fasting glucose 189.56/183.35, HbA1c 8.9/±0.68, 8±0.2, 8).
– After 6 months with exenatide, the weight loss was 2.99±5.12 kg (P<0.01), BMI reduction 1.36±1.18 kg/m² (P<0.0001), of HbA1c 0.84%±2.06 (P<0.05) and of fasting glucose 23.63±1.59 mg/dl (P=0.09).

– After 6 months with Liraglutide, the weight loss was 3.18±3 kg (P<0.05), BMI reduction 1.18±1.67 kg/m² (P<0.05), of HbA1c 0.9%±1.9 (P<0.05) and of fasting glucose 27.31±73.18 mg/dl (P<0.05).
– Greater reduction BMI (0.18±0.77 kg/m²) in the group with Exenatide (P>0.05).
– Greater weight loss (0.19±2.18 kg), greater reduction fasting glucose (21.18±5.86 mg/dl) and a HbA1c greater reduction (0.06%±0.610) in the group with Liraglutide (P<0.05).
– 10 patients (33.3%) had gastrointestinal intolerace in the group treated with Exenatide and 4 (13.33%) in the group treated with Liraglutide (3 gastrointestinal intolerance and 1 dizziess).
– 5 dropouts for gastrointestinal intolerance and insufficient metabolic control in the group with Exenatide and 3 in the Liraglutide group.

Conclusions
Both drugs have very interesting clinical results in both efficiency (comparable to DPP4) and scarce secondary events. Notably Liraglutide currently offers an additional advantage for their a daily dosing.

DOI: 10.1530/endoabs.32.P209

P210
Effect of one session resistance exercise on C-reactive protein and cardio metabolic risk factors in trained and untrained healthy students
Masoume Mansouri, Shirin Hasani-Ranjbar, Abasali Keshhtkar & Bagher Larjani
Endocrinology & Metabolism Research Institute, Tehran University of Medical Sciences, Tehran, Iran.

Introduction
We designed this study, to investigate the effect of a single resistance exercise session on serum C-reactive protein (CRP) and cardio metabolic riskfactors in trained and untrained young healthy male students and to evaluate whether regular training may affect the response of these markers to exercise.

Method
According to training status 34 healthy male students divided to 19 trained and 15 untrained groups. Each group was then randomly divided to intervention and control groups. The final groups included experimental trained (ET), control trained (CT), experimental untrained (EU) and control untrained (CU). The experimental groups underwent exercise training that consisted of 120 min intensive resistance program at 70–80% of 1 RM. The blood samples were collected just before the start of training program and 4 h post exercise to evaluate CRP and other metabolic markers.

Results
ANOVA analysis showed the serum level of blood sugar, insulin, components of lipid profile and CRP were not significantly different between four groups at baseline. More over 4 h post exercise CRP concentration and other cardio vascular riskfactors did not differ between 4 groups. Additionally the paired t-test showed the serum level of CRP and metabolic risk factors was not changed in response to acute resistance exercise in any group.

Conclusion
Our results indicate that one session of acute resistance exercise had no effect on serum concentration of CRP and cardio metabolic risk factors in healthy male students, no matter they were trained or untrained.

Key Words
resistance exercise; C– reactive protein (CRP); cardio metabolic risk factors; trained; untrained.

DOI: 10.1530/endoabs.32.P210

P211
Combination therapy in diabetic patients with insulin glargine and exenatide in the internal medicine service two of hospitals in Valencia
Belen Roig-Espert1, Juan Jose Tamartii-Garcia2, Patricia Sacie-Reyes2, Belen Vizcaino-Castillo2, Ana Ruiz-Garcia1, Amparo Lozano-Cebrian1, Marta Balaguer-Catelan2 & Arturo Artero-Mora1
1Manises Hospital, Valencia, Spain; 2Dr Peset University Hospital, Valencia, Spain.

Background and objective
Combination therapy in diabetic patients is seeking better clinical outcomes by acting on different targets in the pathophysiology of the disease.
Insulin glargine provides excellent glycemic control, especially in the fasting glucose control, in spite of a increasing in weight, compared with exenatide which is more effective in controlling postprandial glycemic and in reducing insulin resistance, plus a reducing effect on the weight.

Design and methods
- Men/Women: 12/18, age 67.36 ± 4.4 years, duration of diabetes 19.6 ± 4.7 years.
- Baseline data: weight 106.51 ± 7.24 kg, BMI 41.25 ± 3.1258 kg/m2, glicated hemoglobin (HbA1c) 8.8 ± 0.61, 64.97 ± gliculated insulin dose 18.64 U/L.
- Changes in insulin requirements U/kg: baseline 0.61 ± 0.18, at 3–6 months 0.39 ± 0.06 and 0.23 ± 0.36 at 9–12 months. Significant reduction in insulin dose: 35.65% at 3–6 months and 48.65% at 9–12 months. Insulin was removed in five patients.
- Changes in weight: all patients lost weight: 4.6 ± 2.73 kg at 3–6 months and 8 ± 6.23 kg at 9–12 months.
- HbA1c evolution: reduced by 83.2% at 3–6 months and 85.3% at 9–12 months. The mean reduction in HbA1c was 0.9 ± 1.03 at 3–6 months and 1.3 ± 1.22% at 9–12 months.
- Tolerance: withdrawal for Exenatide in four patients (13.3%): 2 gastrointestinal intolerance and another 2 by insufficient metabolic control.

Conclusions
The combined use of insulin glargine and exenatide improves glycemic control and in many cases allows the reduction of insulin dose, obtaining further reduction in weight, which makes this partnership a first-choice treatment in of patients with type 2 diabetes and BMI over 30 kg/m2.

DOI: 10.1530/endoabs.32.P211

P212
Metabolic disorders in a group of Algerian hypersonatrotropic subjects
Farida Chentli, Meriem Haddad, Katia Daffeur, Fatima Sararou, Nadia Kalafate, Lina Akkache & Djamil Meskine
Department of Endocrine and Metabolic Diseases, Bab Oued Hospital, Algiers, Algeria.

Introduction
Glucose metabolism disorders are well known in subjects with GH excess, but little is known about other metabolic abnormalities. Our aim is to analyze metabolic complications in subjects with acromegaly and pituitary gigantism.

Subjects and methods
Records of 111 subjects were retrospectively examined, mean GH 26.5 ± 14.7 ng/ml (n ≤ 5), mean age 39.11 (14–60). All had routine analysis for fasting blood glucose, cholesterol, triglycerides, calcium and phosphorus. They all had oral glucose tolerance test (75 g glucose) with glucose measurement during two hours. Hormonal assessment was based on GH and IGF1 (when possible), prolactin, cortisol, ACTH, TSH, FT4, FSH, LH, and testosterone or estradiol (according to their sex). Radiological exploration was based on CT scan, MRI or both.

Results
Among this group 44.8% had gonadotrop deficiency, 22% thyrotrop and 21% corticotrop deficits, because of their pituitary tumours (mean volume 11.4 cm³). Among this group 44.8% had gonadotrop deficiency, 22% thyreotrop and 21% corticotrop deficits, because of their pituitary tumours (mean volume 11.4 cm³). Among this group 44.8% had gonadotrop deficiency, 22% thyreotrop and 21% corticotrop deficits, because of their pituitary tumours (mean volume 11.4 cm³). Among this group 44.8% had gonadotrop deficiency, 22% thyreotrop and 21% corticotrop deficits, because of their pituitary tumours (mean volume 11.4 cm³).

Conclusion
Our subjects, living in a developing country, with GH excess, are at very high risk for cardiovascular diseases because of their metabolic disorders, especially glucose and lipids abnormalities which are higher than recent Poland and Belgium studies in Europe.

DOI: 10.1530/endoabs.32.P212

Clinical case reports – Pituitary/Adrenal
P213
Case report: chronic adrenergic stimulation induces brown adipose tissue differentiation in visceral adipose tissue
Esben Søndergaard, Lars C Gormsen, Steen B Pedersen, Peer Christiansen, Søren Nielsen, Per L Poulsen & Niels Jessen
Aarhus University Hospital, Aarhus, Denmark.

Introduction
The presence of brown adipose tissue (BAT) in humans has recently been demonstrated by histology and positron emission tomography (PET). In previous reports, BAT in adults is primarily confined to the upper chest and neck. Here, we report a case of massive BAT infiltration of the visceral adipose tissue in a patient with catecholamine secreting paraganglioma.

Methods
The patient was evaluated with [18F]-FDG PET/CT at three occasions: pretherapy, during α-blockade and postoperatively. During surgery, biopsies of visceral and subcutaneous adipose tissue were obtained. Histological specimens were evaluated for BAT and uncoupling protein 1 (UCP-1) gene expression was verified by QPCR, WB and immunohistochemistry. Resting energy expenditure was measured with indirect calorimetry.

Results
At diagnosis, BAT glucose uptake assessed by FDG PET was massively increased (see figure). FDG uptake was confined to known locations for BAT with additional uptake in the visceral adipose tissue. No excess activity was observed in subcutaneous adipose tissue. Histological examination revealed areas of BAT in the visceral adipose tissue with ~200-fold greater UCP-1 gene expression compared to subcutaneous adipose tissue. Owing to increased thermogenesis, resting energy expenditure was 15 188 kJ/day at diagnosis with a decrease to 8368 kJ/day after surgery. During α-adrenergic receptor-blockade, FDG uptake was decreased (see figure). After surgical removal of the tumor, BAT FDG uptake returned to normal (see figure). Normetanephrine level was greatly increased at diagnosis, with normalization after surgery (diagnosis: 3318 ng/l; post-surgery: 132 ng/l (< 200 ng/l)).

Conclusion
In this case report, chronic adrenergic stimulation increased BAT differentiation and activity in visceral adipose tissue. Stimulation of adrenergic receptor signaling in BAT progenitor cells may have promising perspectives for future treatment of obesity and type 2 diabetes.

Figure 1
DOI: 10.1530/endoabs.32.P213

P214
An unusual case of Cowden-like syndrome, neck paraganglioma and pituitary adenoma
Zoe Efstathiadou, Panagiotis Anagnostis, Michalis Sarianidis & Marina Kita
Department of Endocrinology, Hippokration Hospital of Thessaloniki, Thessaloniki, Greece.

Introduction
The description of a rare case of papillary thyroid cancer, neck paraganglioma, pituitary adenoma and Cowden-like syndrome.

Case report
A 43-year-old woman presented with enlargement of her right thyroid lobe and a palpable ipsilateral neck mass. The pathology examination after operation of the two lesions revealed the synchronous presentation of a papillary thyroid carcinoma and a neck paraganglioma. Patient’s medical history included a microprolactinoma, diagnosed one decade before and a constellation of characteristics that are components of Cowden syndrome, specifically an excised mammary gland fibroadenoma on grounds of fibrocystic disease and a large uterine leiomyofibroma under observation. Physical examination revealed macrocephaly and multiple skin papules.

Germline mutation analysis of PTEN, SDHB, SDHC and SDHD was performed with revelation of 3 polymorphic sites in introns 1, 4, 8 of PTEN gene and 1 polymorphic site in exon 1 of SDHB gene, but absence of known pathogenic mutations.
P215

Follicle-stimulating hormone-secreting pituitary macroadenoma: a rare cause of abnormal menstrual cycles in a teenage girl

Birsen Arici1, Stefan Moto1,2, Christopher Kelly1,2, Henryk Zulewski1 & Luigi Mariani1
1Department of Endocrinology, University Hospital Basel, Basel, Switzerland; 2Department of Neurosurgery, University Hospital Basel, Basel, Switzerland.

Introduction
Gonadotroph adenomas usually present as clinically non-functioning sellar masses. They are rarely infrequent in children. Only some case report of children and adolescents with clinical manifestations of high serum gonadotroph levels have been published. As in adult patients most of the gonadotroph adenomas have a silent growth, and therefore a late presentation as macroadenoma with mass effects.

Case report
This 16-year-old girl presented with menorrhagia, polynorhagia and galactorrhea. Menarche had occurred at 11 years of age and initially menses were regular. The patient reported a high frequent and prolonged menstrual bleeding since one year. A gynaecological examination revealed multicystic right ovary without other pathological findings and a gestagen-only pill was prescribed. After starting this treatment an oligomenorrhea with menstrual bleeding every two month occurred. Nine month later the patient developed galactorrhea and prolactin was slightly elevated with 1117 mU/l (reference 530 mU/l). With suspicious for prolactinoma a therapy with bromocriptin was initiated and a radiological evaluation showed following laboratory parameters: LH 492 U/l (76–492), FSH 23 U/l (0.5–417), IGF1 39.4 nmol/l (25.1–95.0), fT4 16.1 pmol/l (12.6–21.0), TSH 4.0 mIU/l (0.5–4.0), and cortisol 506 nmol/l (80–638). At this time she had on-going menstrual bleeding for the last 3 weeks and no current medication. Elevated estradiol and FSH and suppressed LH was compatible with FSH-secreting pituitary adenoma. The somatotroph, thyreotroph and corticotroph axes were preserved and no disturbance of the water balance was noted. Hyperprolactinemia was interpreted as consequence of high estradiol levels and pituitary stalk compression. The postoperative course was uneventful except for a possible rhinoliquorrhea which resolved after 3 days of lumbar CFS drainage. The histopathological evaluation confirmed the diagnosis of atypical pituitary adenoma and showed immunohistochemical positivity for FSH in numerous cells. One month later normal menstrual cycle resumed and endocrine tests showed normal laboratory parameters.

Conclusion
In this case of FSH-producing pituitary adenoma, the medical history of on-going menstrual bleeding associated with highly increased estradiol, high FSH and suppressed LH were the diagnostic hallmarks. The presence of polycystic ovaries is also typical for this condition. The slightly elevated prolactin level was initially misinterpreted as evidence for prolactinoma that would have presented with much higher values in a 26 mm adenoma.

P216

Long-term treatment with octreotide in a patient with malignant pheochromocytoma: impact on survival and time to tumor progression

Anna Gruszko1, Wojciech Zieniwnski1, Agnieszka Koteka-Blicharz1, Barbara Jarzab & Jolanta Kunert-Radek1
1Department of Endocrinology, Medical University of Lodz, Lodz, Poland; 2Department of Nuclear Medicine and Endocrine Oncology, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Gliwice, Poland.

Introduction
Pheochromocytomas are rare neuroendocrine tumors arising from chromaffin cells of the adrenal medulla. Approximately 10% of all pheochromocytomas are malignant. There is no effective therapy for malignant pheochromocytoma (MAL-PHEO) and the overall prognosis is poor.

Case report
We report 22-year survival with MAL-PHEO in a patient treated with several surgeries, 131I-metaiodobenzylguanidine and, subsequently, with long-acting formulation of octreotide (octreotide-LAR) for 10 years. In 1990, a 43-year-old woman was diagnosed with pheochromocytoma. She underwent left radical nephrectomy and adrenalectomy in 1990. In 1993 and 1995, the patient underwent subsequent operations because of the tumor recurrence. In 2002, metastases in the thoracic vertebrae with a compression on the dural sac were found and the patient underwent surgical decompression in 2002 and 2004. At referral to our Department in 2002, patient’s serum chromogranin A was 342 U/l (normal range: 2–18 U/l). Somatostatin receptors scintigraphy with 99mTc-EDDA/HYNIC-TOC revealed multiple vertebral and lymph nodes metastases with high expression of somatostatin receptors. In February 2003, the therapy with octreotide-LAR (20 mg i.m. every 28 days) was started. In 2004/2005 the patient was treated with 131I-metaiodobenzylguanidine with a partial radiological and complete biochemical tumor response. The therapy with octreotide-LAR has been carried on from 2003 until the present time. Until 2010 radiological and biochemical stabilization of the disease had been observed. In 2010 the presence of lung metastases was revealed. Patient’s serum chromogranin A increased (286 U/l in September 2012), however 24-hour urinary excretion of metanephrines is within normal range. Currently, the patient is under consideration for the treatment with radiolabeled octreotide derivates.

Conclusions
This is the first report of long-term treatment with octreotide in a patient with MAL-PHEO. Our findings suggest that, as it has been recently shown in patients with metastatic midgut neuroendocrine tumors, the treatment with octreotide-LAR may prolong survival and time to tumor progression in patients with MAL-PHEO.

P217

Histologically surprising nasal polyps

Marina Boscolo, France Devuyst & Bernard Corvilain
CHU Erasme, Brussels, Belgium.

Pituitary macroadenomas usually present with symptoms due to a local mass effect or to hormone abnormalities. Acromegaly is due an excessive GH production, usually caused by a slow-growing pituitary adenoma. Acromegaly is an insidious disease. An average delay of 7 years is reported between the time of symptoms onset and diagnosis. According to main symptoms, acromegaly is usually diagnosed by internists, ophthalmologists or rheumatologists. It may be suspected by pneumologists in case of sleep apnea syndrome. Only exceptionally otorhinolaryngologists diagnose the disease, even if nasal polyps may be present in up to 5% of patients. We discuss here the unusual case of a 34-year-old woman who presented to an otorhinolaryngologist with persistent nasal congestion and forehead pain, unresponsive to antibiotic and anti-inflammatory treatment. Nasal endoscopy confirmed the presence of nasal polyps. Computed tomography of paranasal sinuses showed massive mucosal hypertrophy with a voluminous polyoid intranasal lesion. Transnasal biopsy demonstrated the presence of pituitary tissue. Hormonal evaluation showed a very high serum IGF-1 (1185 ng/ml) and an increased serum growth hormone (48 ng/ml), leading to the diagnosis of acromegaly. The patient underwent transphenoidal surgery and histology confirmed the presence of a GH secreting adenoma. Intranasal presentations of pituitary tumours are uncommon. This case illustrates that pituitary lesions may present as polyps invading nasal cavities. To our knowledge only ten cases have been reported in literature (seven macropituitomas, two nonsecreting adenomas and one macroadenoma with ACTH immunopositivity). In all the reported cases initial diagnosis was that of a nasal polyp or of an intranasal carcinoma. We conclude that in a patient with nasal polyps, looking for clinical signs of Cushing syndrome or of acromegaly and subsequent hormonal evaluation could be of help for an early diagnosis.

DOI: 10.1530/endoabs.32.P217
15th European Congress of Endocrinology 2013

Endocrine Abstracts (2013) Vol 32

P218 Hypopituitarism and pituitary masses in patients with non-pituitary malignancy
Saifuddin Kassim1, Josh Wright2, Bernie Foran3, Saurabh Sinha3, John Newell-Price2 & Richard Ross1
1Department of Endocrinology, Royal Hallamshire Hospital, Sheffield, UK;
2Department of Haematology, Royal Hallamshire Hospital, Sheffield, UK;
3Department of Neurosurgery, Royal Hallamshire Hospital, Sheffield, UK;
4Department of Oncology, Western Park Hospital, Sheffield, UK.

The commonest cause of acquired hypopituitarism is a benign pituitary adenoma. However, in patients with non-pituitary malignancy different diagnoses need to be considered. We describe three oncology patients presenting with hypopituitarism and/or a pituitary mass where the cause was related either to malignant disease or its treatment.

Case 1
A 56-year-old man with known metastatic melanoma presented with increasing lethargy. Investigation showed a large heterogeneous mass in the suprasellar region with a displaced normal enhancing pituitary gland. The mass was thought to be melanoma metastasis, and showed significant reduction in size (more than 70%) following treatment with vemurafenib, a RAF kinase inhibitor.

Case 2
A 62-year-old man with known metastatic melanoma presented with fatigue and was found to have hypopituitarism (Ft4 – 5.0 pmol/l, TSH – 0.15 mIU/l, Cortisol – 13 mmol/l, Prolactin – 121 mIU/l, Testosterone – <0.4 nmol/l, LH – 1.5 IU/l, FSH – 2.5 IU/l). MRI scan of the pituitary was normal. The patient was on Ipilimumab (human monoclonal antibody directed against cytotoxic T lymphocyte antigen 4 (CTLA-4)), which has been reported to cause hypopituitarism secondary to hypophysitis (Hodi et al. New England Journal of Medicine 363 711, 2010).

Case 3
A 73-year-old woman with diffuse large B cell non-Hodgkin lymphoma (DLBCL) presented with third nerve palsy and lethargy. MRI showed a large pituitary lesion thought to be either lymphoma or a pituitary macroadenoma. The pituitary lesion showed near complete shrinkage following three cycles of CHOP-R chemotherapy.

These three cases illustrate that patients with non-pituitary malignancy presenting with hypopituitarism may include metastasis and side effects from treatment of the primary malignancy including hypophysitis.

DOI: 10.1530/endoabs.32.P218

P219 Wegener granulomatosis as an uncommon cause of panhypopituitarism in childhood
Fatma Demirel1, Ozlem Kara1, Banu Celikel Acar1,2 & Nilgun Cakar1,2
1Department of Pediatric Endocrinology, Ankara Child Disease Hematology and Oncology Training Hospital, Ankara, Turkey; 2Department of Pediatric Nephrology, Ankara Child Disease Hematology and Oncology Training Hospital, Ankara, Turkey.

Wegener granulomatosis is an antineutrophil cytoplasmic antibody (cANCA)-associated, multi-system, necrotizing granulomatous vasculitis. Inflammation of nasal or oral mucosa, lung and kidney involvements are typical in the course of the disease. It was first described by Friedrich Wegener in 1939, and has an incidence rate of 1 in 100 000 people, often observed in individuals aged between 25 and 50 years, but uncommon in children and adolescent. In rare cases, pituitary involvement is very rare especially in pediatric population. This is a case report of an adolescent patient who presented with panhypopituitarism symptoms and was later diagnosed with WG. Sixteen years-old female patient complained fever, headache, purulent nasal discharge and severe muscle and joint pain. Additionally she had polyuria and polydipsia. Investigations revealed pituitary mass and panhypopituitarism. The MR imaging showed a high-signal-intensity mass, which had a height of 15–19 mm, suspicious necrotic hemorrhagic regions, thickening of the pituitary stalk, hyperintense of the neurohypophysis. Positivity of c-ANCA and renal biopsy result compatible with Wegener’s granulomatosis confirmed the diagnosis.

The patient was started on conventional treatment, which leads to the shrinking of the granuloma in the pituitary gland. A relapse did not occur over the one-year follow-up period, and the patient was still under hormone replacement therapy. WG should be considered in pediatric patients with panhypopituitarism symptoms when suspected of a granulomatous disease due to the involvement of other organs. Necrotic granulomatous lesions in MR imaging of the pituitary and ANCA positivity serve as guides in WG diagnosis.

DOI: 10.1530/endoabs.32.P219

P220 Adequate timing for adrenalectomy in pheochromocytoma multisystem crisis: can early biochemical diagnosis be the key?
Manuel Cayon1, Carolina Garcia-Figueras2, Anselmo Gil3 & Francisco Mateos4
1Endocrinology and Nutrition Unit, Hospital SAS, Jerez de la Frontera, Spain; 2Internal Medicine Unit, Hospital SAS, Jerez de la Frontera, Spain; 3Intensive Care Unit, Hospital SAS, Jerez de la Frontera, Spain; 4General and Digestive Surgery Unit, Hospital SAS, Jerez de la Frontera, Spain.

Introduction
Pheochromocytoma multisystem crisis (PMC) is the most fulminant clinical expression of pheochromocytoma. The appropriate timing and judgment for the start of surgery and the adequate preoperative medical treatment are unclear. We report a case of PMC successfully treated with elective adrenalectomy after doxazosin blockade. The importance of an early biochemical diagnosis is discussed.

Case report
A 47-year-old healthy man consulted for sudden onset dyspnea and thoracic discomfort. In the Emergency Department, his level of consciousness upon arrival was 12 (Glasgow Coma Scale) and he was found to be in acute respiratory distress with severe hypoxemia, requiring intubation in Intensive Care Unit. His blood pressure was 165/110 mmHg and his body temperature, 39.9 ºC. Electrocardiography revealed atrial flutter. The laboratory data showed polycythemia, severe renal and hepatic failure, rhabdomyolysis and hyperglycemia. All infectious screens were negative. A blood sample drawn on the patient’s arrival at the hospital showed high serum norepinephrine (>758 pg/ml; normal <370). Epinephrine and dopamine concentrations were normal. An abdominal CT scan revealed a 3 cm. Mass, located in the right adrenal gland and a MIBG scan was strongly positive. After reaching clinical stability, elective right laparoscopic adrenalectomy was performed under previous β-blockade with doxazosin.

Pathology examination revealed a 3 cm. Pheochromocytoma without evidence of malignant involvement, necrosis or haemorrhage. Six months after, he is asymptomatic and his level of catecholamines is normal.

Conclusions
Most reported PMC cases requiring emergency surgery or died were mixed producers of epinephrine and norepinephrine or epinephrine only. The high rate of initial suspicion allowed us an early identification of amine secreted by the tumour and it allowed us to plan a specific therapeutic strategy. Future studies with a major number of cases are needed; nevertheless our observation suggests that pure norepinephrine secretor tumours may have a more favourable clinical course and this knowledge could help to identify candidates to elective surgery after doxazosin blockade.

DOI: 10.1530/endoabs.32.P220

P221 Complex hypothalamic disorder after childhood histiocytosis X
Monica Livia Gheorghiu1,2, Anda Carageaheorgheopol1, Anda Dumitrascu1 & Catalina Potain1
1C.I. Parhon1 National Institute of Endocrinology, Bucharest, Romania; 2C. Davila’ University of Medicine and Pharmacy, Bucharest, Romania.

Introduction
Histiocytosis X is a rare disease involving clonal proliferation of Langerhans cells, abnormal cells deriving from bone marrow and capable of migrating from skin to lymph nodes. Its manifestations range from isolated bone lesions to multisystem disease. Seen mostly in children, multifocal histiocytosis may involve in 50% of cases the pituitary stalk, leading to diabetes insipidus and...
usually permanent pituitary deficiencies. We present an adult patient with a complex hypothalamic–pituitary disorder after histiocytosis X in childhood.

Case presentation
A 28 years old female has been diagnosed at the age of 4 with histiocytosis X and treated for 1 year with prednisone. She has had since diabetes insipidus treated with desmopressine and hypothyroidism treated with 50 µg thyroxine. She had grown until the age of 10 when she achieved the current height of 151 cm, her parents' heights being 170 and 180 cm. She had normal menarche with menstrual cycles of 40 days. Clinical examination revealed only slight overweight and polyuria after desmopressin withdrawal.

Hormonal evaluation (after 6 weeks thyroxine withdrawal) showed hypothyroidism FT4 0.61 ng/dl (0.7–1.4), TSH 5.2 mUI/l (0.35–4.94), ATPO 0.45 UI/ml (<0.6I), normal FSH 5.06 mUI/ml, LH 2.97 mUI/ml, PRL 19.69 ng/ml (5–26), low day-21 progesterone 0.1 ng/ml (2–24) suggesting chronic anovulation, normal basal and stimulated cortisol (16.4 and 22.9 µg/dl), severe GH deficiency IGF1 29.2 ng/ml (117–329), peak GH in insulin-induced hypoglicemia = 0.1 ng/ml. The dehydration test confirmed central diabetes insipidus. Thyroid sonography was normal. CT scan showed empty sella and pituitary hypoplasia.

Discussion
A peculiarity of this patient is the continuous linear growth for another 6 years after diagnosing histiocytosis, suggesting a late and perhaps progressive GH deficiency. In the absence of thyroid autoimmunity, the slightly increased TSH has probably low bioactivity, as described in central hypothyroidism.

Conclusion
Histiocytosis X in children may lead to a complex hypothalamic disorder persistent into adult life, including diabetes insipidus, severe (sometimes progressive) GH deficiency, hypothyroidism and chronic anovulation.

DOI: 10.1530/endoabs.32.P222

P222
Morphological and functional abnormalities of the hypophyse in patients with diagnose of CFS or fibromyalgia. An example of misdiagnosis by Belgian chronic fatigue centres
Francis Coucke, Heidi Lammens, Laurens Coucke & Anne-Birgitte Vogter
METARES, Sint Gillis Was, Belgium.

Aim
In consultation, we check a lot of patients who present with diagnose of FM (fibromyalgia) and chronic fatigue syndrome (CFS). Most of these patients have a underlying diagnosis that causes chronic pain or fatigue. These causes are pathologies not easily detected.

Endocrine failure is one of the candidates, with hypophyse dysfunction as a possible candidate.

Methods
During 1 year: from October 11, 487 patients presented at the consultation we offered to patients by treating the underlying hormonal deficiencies.

Results
Forty seven patients with abnormalities of the hypophyse:
- Cysts: 6 cases average age 50.8, all female, mean diameter 5.2 mm (from 4 to 8 mm). All are ACTH–cortisol deficient and 1 of them is GH deficient (GHD).
- Adenomas: 31 cases average age: 42 years, 23 female, 8 males, mean size of 5 mm (from 12 to 3 mm), all are ACTH–cortisol deficient and 11 are also GHD.
- Empty cells: 12 cases: average age: 53, 25 years, 5 males, 7 females, all deficient in ACTH–cortisol and 8 are GHD.

Conclusion
Patients with a diagnose of CFS or fibromyalgia should always be checked for underlying chronic diseases. Mostly immunologic but also endocrine diseases can be underlying. E.g. frequently adrenal insufficiency can be detected. A lot of reports document also a low IGF1 and GHD.

Patients with hormone deficiencies should also be checked for other hormone deficiencies. In case of low hypophyse hormones, single or multiple, the hypophyse has to be functionally and morphologically checked. On contrary with the disappointing general therapy of FM or CFS, a good and efficient therapy can be offered to patients by treating the underlying hormonal deficiencies.

DOI: 10.1530/endoabs.32.P222

P223
Pineal gland tumor and panhypopituitarism in an adult male
Queenie Ngalob & Gabriel Jasl
Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, Philippine General Hospital, University of the Philippines, Manila, The Philippines.

Background
Pineal germ cell tumors are rare in adulthood. It usually comes to medical attention due to mass effect. Endocrine manifestations are also prominent in the clinical presentation and may preclude neurologic symptoms.

Clinical case
We report the case of a 30-year old male who presented with a 6-month history of bitemporal headache, doubling of vision and nonprojectile vomiting. Recall revealed that he exhibited symptoms of panhypopituitarism as early as two years prior. He also had excessive thirst, polyuria and nocturia. Five months upon presentation, he developed rapidly progressive pain then numbness of both lower extremities which eventually culminated in loss of motor strength and sensation.

Physical examination showed limitation of vertical movements of both eyes, paraplegia and hypoesthesia of both lower extremities.

Investigations confirmed anterior pituitary failure with central hypothyroidism, adrenal insufficiency, hypogonadism and diabetes insipidus. Tumor markers alpha-fetoprotein and beta HCG were elevated. Imaging revealed obstructive hydrocephalus and a 5.8×5.4×4.6 cm pineal gland tumor with normal sella. Magnetic resonance imaging of the spine showed spinal cord lesions and leptomeningeal enhancement. A diagnosis of pineal nongerminomatous germ cell tumor with spinal cord and leptomeningeal carcinomatosis was made.

Hormonal deficiencies were replaced with oral l-thyroxine, prednisone and desmopressin.

The patient underwent cranial irradiation which resulted in more than 50% regression in the tumor size. Spinal radiotherapy yielded sensory but no motor recovery. Chemotherapy was initiated using bleomycin, etoposide and cisplatin.

He developed nosocomial pneumonia and febrile pneumonia 1 week later to which he succumbed.

Conclusion
The characteristic clinical triad of diabetes insipidus, anterior pituitary failure and visual disturbances is a harbinger of a pineal germ cell tumor. It may present with panhypopituitarism even in the absence of pituitary involvement on imaging. Thorough endocrine evaluation and hormone replacement is essential in its management.

DOI: 10.1530/endoabs.32.P223

P224
Antepartum pituitary insufficiency in type 1 diabetes
Chandima N D Balasuriya, Stine Lyngvi Fougner & Marit Rokne Bjørgaas
St Olavs Hospital, Trondheim, Norway.

Introduction
Postpartum necrosis of the anterior pituitary gland is well-described, but antepartum pituitary insufficiency (API) is reported only in a few women with type 1 diabetes (T1D). API has an abrupt onset and may have fatal outcome.

Case report
A 36-year-old woman with T1D and laser-treated retinopathy became pregnant after repeated IVF. In gestational week (GW) 10, she used insulin 34–42 U/day, HbA1c was 6.2% and cortisol (0800 h) was 664 nmol/l. In GW 34, she was hospitalized with intense headache and vomiting. On admission, plasma glucose was 2.6 mmol/l. Neurological examination, CSF and cerebral MRI, were normal. She had no sign of preeclampsia. Insulin doses were reduced. At 0800 h. cortisol was 144 nmol/l, ACTH <1.1 pmol/l, prolactin 285 mUI/l, GH 1.5 mUI/l, indicating pituitary failure. She was treated with i.v. glucose and hydrocortisone.

An emergency Caesarean section was performed, without excessive haemorrhage. She was notoensive. The newborn’s weight was 2610 g and Apgar score 9 (1 min). Three days postpartum (PP) pituitary MRI was normal. She was unable to breastfeed. Two months PP, insulin tolerance test (ITT) showed subnormal cortisol and ACTH responses (436 nmol/l and 2.8 pmol/l, respectively). Despite substantial reduction in insulin dose and low-dose cortisol replacement, she experienced frequent hypoglycaemias without warning. Repeated MRI at three
months PP revealed reduced contrast uptake in the pituitary consistent with necrosis. ITT after 2 years showed subnormal responses of both cortisol (peak 468 nmol/l) and GH (peak 4.5 mU/l). GH replacement improved her hypoglycaemia awareness and her general well-being.

Conclusion
The hypertrophied pituitary of late pregnancy may be vulnerable to infarction and necrosis. We speculate whether repeated ovarian stimulation together with microvascular diabetic complications may have increased the vulnerability to thromboembolism and subsequent pituitary infarction in this woman with API.

DOI: 10.1530/endoabs.32.P224

P225
Delivery of health child in acromegaly patient with McCune–Albright syndrome treated with lanreotide and pegvisomant during pregnancy
Vladimir Weiss, Vaclav Hana & Josef Marek
3rd Department of Internal Medicine, University Hospital, Prague, Czech Republic.

Introduction
Acromegaly with GH excess affects up to 20% of the patients with McCune–Albright syndrome (MAS). Surgical treatment for acromegaly in MAS is often difficult because of skull-base dysplasia. Somatostatin analogs are frequently only partially effective and GH receptor antagonist – pegvisomant is more potent in normalizing IGFI levels. Radiotherapy is controversial. Pregnancy in MAS patients is described in literature but no case of successful delivery in MAS patient with acromegaly treated with both somatostatin analog and pegvisomant was published till now. Only three cases of pegvisomant treated pregnant acromegalic patients have been published (two with medication throughout the whole pregnancy).

Case report
At the age of 32, diagnosis of MAS with multiple endocrine disorders (acromegaly, peripheral hyperthyroidism, hyperparathyroidism) was diagnosed. Neurosurgery and/or irradiation was not possible due to serious osteosclerotic in sellar region and medicament treatment was started using long-acting somatostatin analogue lanreotide, which was later combined with GH antagonist pegvisomant. At the age of 36, woman became pregnant. The patient insisted on pregnancy. We continued lanreotide and pegvisomant treatment. Pregnancy and delivery was not complicated and healthy girl was in 38th week of gestation born (cesarean section). Lactation was blocked. Further development of this girl is normal. We continue with lanreotide and pegvisomant treatment.

Conclusion
We report successful pregnancy in an acromegalic patient with MAS treated by combination of pegvisomant and lanreotide. Child’s weight and length was lower, influence of therapy by lanreotide and pegvisomant can be discussed. Father’s body constitution could have some influence as well. No congenital malformations were present, development is physiological, there are no signs of endocrine/bone disorders.

DOI: 10.1530/endoabs.32.P225

P226
Intrasellar plasmacytoma: an unusual presentation of multiple myeloma
Ayse Akkurt, Pınar Sisman, Canan Ersoy, Erdinc Erturk, Ercan Tuncel & Sazi Imamoglu
Uludag University Medicine School, Bursa, Turkey.

Multiple myeloma is a neoplastic disorder arising from plasma cells in the bone marrow. Plasma cell tumors, plasmacytomas, are uncommon in the brain and occur usually in the leptomeninges with or without parenchymal involvement.

Extramedullary plasmacytomas are very rarely located in the sella and can be misdiagnosed as a nonfunctioning pituitary adenoma. We report an illustrative case with multiple myeloma who was diagnosed having sellar plasmacytoma resembling a nonfunctioning pituitary adenoma. A 56-year-old Caucasian woman presented with a history of headache and diplopia. She denied any other neurological symptoms. Her complaints started approximately 6 months ago. She had a mild anemia with a hemoglobin level of 11.1 g/dl (12–14 g/dl). Blood chemistry analyses were normal. Serum prolactin level was slightly elevated at 76.44 ng/ml (1.2–29 ng/ml), but other hypothalamic hormones were within normal limits. Magnetic resonance imaging (MRI) of the brain showed a 26×22×31 mm mass destroying the floor of sella and infiltrating the clivus. The presumptive diagnosis was of a nonfunctioning pituitary adenoma and transphenoidal pseudocystic was performed. The histological appearance of the specimen was that of a highly cellular neoplasm composed of mature plasma cells with round eccentrically located nuclei. Immuno-cytchemistry showed that all the tumor cells were positive for CD 138 and lambda light chains confirming that this tumor was a plasmacytoma. Post operatively an extensive investigation for myelomatous disease was undertaken including serum and urine protein electrophoresis, a bone survey and a bone marrow biopsy. Serum protein electrophoresis detected a monoclonal gammopathy with IgG kappa type M protein on serum immunofluorescence electrophoresis. Urine was negative for Bence-Jones proteinuria. Beta 2 microglobulin level was 3.2 mg/dl. Bone marrow biopsy showed plasma cell infiltration. The diagnosis of multiple myeloma with involvement of the pituitary gland was made. Subsequently, systemic chemotherapy consisting of melphalan and prednisone was given for 6 cycles. The patient remained in remission for 20 months after the therapy.

In conclusion, although multiple myeloma involving pituitary gland is rare, it must be considered in the differential diagnosis of a nonfunctioning pituitary mass. A hypophysial mass with a normal anterior pituitary hormonal profile should alert the physician for the possibility of a diagnosis other than a chromophobe adenoma.

DOI: 10.1530/endoabs.32.P227
P228
Xanthomatous hypophysitis as a cause of cluster headache: a case report
Éva Csapók1, Sándor Magony1, Kirsztian Sepp1, Zsuzsanna Valkusz1, Pál Baricz2 & László Tiszai2
1 lst Department of Internal Medicine, University of Szeged, Szeged, Hungary; 2Department of Neurosurgery, University of Szeged, Szeged, Hungary; 3Department of Pathology, University of Szeged, Szeged, Hungary.

Introduction
Hypophysitis is an inflammatory disease of the pituitary gland that may mimic pituitary tumors clinically and radiologically. Primary hypophysitis has traditionally been classified as lymphocytic (LH), granulomatous (GH), and xanthomatous (XH).

Case description
We report on a case of a xanthomatous hypophysitis initially diagnosed as pituitary adenoma. A 23-year-old man suffered from typical cluster type headache. Two years after the first symptoms, we confirmed diabetes insipidus in the background of polyuria-polydipsia. All the anterior pituitary hormone levels were normal. Head MRI scan depicted a 14 × 10 × 17 mm inhomogeneous mass in sella. Transphenoidal surgery was performed; the removed tissue showed by accumulation of foamy cells and xanthomatous epitheloid cells. The patient had an uneventful postoperative recovery. After surgery, we tried to stop the hydrocortisone therapy but severe cluster type headache returned. The endocrine work up revealed hypoadrenalinemia (morning cortisol: 96 nm/l, ACT: 3.38 pm/l), hypothyroidism (T4: 10.5 pm/l), hypogonadism (testosterone: 3.44 nm/l) with normal FSH and LH (FSH: 3.3 mIU/l, LH: 2.8 mIU/l). We restarted hormonal therapy: hydrocortisone, l-thyroxine and testosterone were stepwise reintroduced. During the follow-up period we could stop the hydrocortisone and l-thyroxine supplementations, whereas the patient has permanently required desmopressine and testosterone substitution. Because of his hypogonadism after pituitary surgery, the patient was sent for sperm storage. Control sella MRI scans revealed no progression of the initially seen pituitary tumor.

Conclusion
We describe an unusual case of xanthomatous hypophysitis causing cluster type headache and permanently requiring ddAVP (desmopressine) and testosterone supplementation however, without need for maintenance medication with hydrocortisone and l-thyroxine.

DOI: 10.1530/endoabs.3.P228

P230
Very late growth acceleration in a man with hypopituitarism
Agnieszka Sawicka1,2, Dorota Boniek-Poprawa1,2, Agnieszka Kawalko2, Marta Wegrzyn-Bak2 & Krzysztof Marczukiewicz1,2
1University of Management and Administration, Zamosc, Poland; 2John Paul the II Regional Hospital, Zamosc, Poland.

Introduction
Very late step growth is quite rare, and probably very rare, if there is, 10 years after the end of treatment with GH. Therefore, we would like to present our patient, even though we cannot yet give a full pathomechanism of his disorders.

Case report
A man 28 years was admitted to us to assess hormonal status before elective hip surgery. He had congenital brain toxoplasmosis. From 8 to 16 years he was treated with GH without a good effect. However, in the last 2 years, so between 26 and twenty eight years, he has grown more than 20 cm. Laboratory results indicated hypopituitarism with undetectable GH and low IGF1, adrenal insufficiency (cortisol 18 μg/l, ACTH 21 ng/l), and hypothyroidism (FT4: 7.2 pmol/l) and TSH 5.8 mU/l) and hypogonadism with undetectable testosterone levels and LH <0.20 mU/l, FSH 0.4 mU/l and estradiol 29 pg/ml. In inguinal canal and scrotum, we found small fragments of glandular tissue. The response to gonadotropin was week. In MRI normal pituitary 5 × 6 × 9 mm, and at the bottom of third ventricle 5 mm size, expansive tissue. No signs of puberty, height 174 cm, weight 54 kg BMI 17.8. The ephiphyses are not fused together and the patient is still growing despite the very low IGF.

Adrenal replacement therapy was started followed by thyroid replacement therapy. We consider the operations to remove the glandular tissue of the inguinal canal and scrotum and substitutions with testosterone.

Discussion
We take into account the possibility of ectopic secretion of IGF other than growth factors and/or factor causing sensitivity to IGF. However, this remains speculation. Therefore, we would like to present him hoping for help from the European Endocrinologists.

DOI: 10.1530/endoabs.3.P230

P229
Primary adrenal insufficiency in a case of bilateral adrenal hemorrhage secondary to anti-phospholipid syndrome masquerading as chronic abdominal pain
Abel Weiliang Chen, Cheng Jye Seow & Rinkoo Dalan
Tan Tock Seng Hospital, Singapore, Singapore.

Background
Primary adrenal insufficiency due to adrenal hemorrhage from anti-phospholipid syndrome (APS) is an uncommon and life threatening disorder. We present a case, highlighting the challenges in the diagnosis and management of this disorder.

Case presentation
A 59-year-old Chinese lady presented with a 2-year history of bilateral flank pain, lethargy, poor appetite and weight loss. Initial blood investigations were unremarkable except for a cholestatic liver function test. A computed tomography of the abdomen incidentally revealed bilateral adrenal hemorrhages. She had not sustained any trauma, did not have a bleeding disorder and was not taking any anticoagulants. Subsequent workup confirmed the diagnosis of primary APS with elevated levels of lupus anticogulant, anticardiolipin and anti-B2 glycoprotein.

She did not have any other associated connective tissue disorders or malignancies. Thrombophilia screen was normal. There was concomitant primary adrenal insufficiency with a blunted synacthen test response. Cortisol was 35 mmol/l at 0 min and 34 mmol/l 30 min after synacthen was given; ACTH was markedly elevated at 194 pmol/l. Aldosterone was undetectable while renin was elevated at 4.96 ng/ml per hour. She was started on hydrocortisone and fludrocortisone in addition to anticoagulation. Interval adrenal imaging showed near complete resolution of adrenal hemorrhage but the adrenal insufficiency persists with undetectable aldosterone despite 1 year of follow up.

Conclusion
Clinicians need to have a heightened awareness of the association between adrenal hemorrhage and APS and institute treatment early. Despite radiological resolution of the adrenal hemorrhage, adrenal insufficiency persists, likely secondary to irreversible hemorrhagic infarction of adrenal tissue.

DOI: 10.1530/endoabs.3.P229

P231
Differential diagnosis of aggressive macroprolactinoma, adenoma or atypical adenoma: a case report
Fatima Neslihan Cubaci1, Huseyin Baser1, Mehmet Faik Ozveren2, Sultan Cigdem Ikkan3, Hayriye Tatlı Dogan4, Reyhan Eroş5 & Bekir Çakır6
1Department of Endocrinology and Metabolism, Atatürk Education and Research Hospital, Ankara, Turkey; 2Department of Neurochirurgie, Atatürk Education and Research Hospital, Ankara, Turkey; 3Department of Pathology, Atatürk Education and Research Hospital, Ankara, Turkey; 4Department of Endocrinology and Metabolism, Yıldırım Beyazıt University, Ankara, Turkey.

Atypical tumors were identified in 15% of pituitary adenomas, and they tended to be aggressive, invasive macroadenomas. WHO classification of atypical pituitary adenomas include: Ki-67 proliferative index >3%, excessive p53 immunoreactivity, and ≥2 mitotic figures per 10 high-powered fields. Pituitary carcinomas are extremely rare tumors with cerebrospinal or extracranial metastasis.

Case
A 31 years old man with symptoms of stuffy nose and snore, presented to our polyclinic due to the solid lesion on parasinal sinus tomography. Tomography showed a soft tissue lesion with 38 Haunsfield Unit (HU). Pituitary imaging revealed a mass, which lead to destruction of bone structures, suppression of optic chiasm, extending to suprasellar cistern and right nasal cavity. Except increased prolactin (470 ng/ml) hormonal levels were within normal ranges. Macroprolactin was negative. Nasal punch biopsy showed an atypical pituitary adenoma with atypical and 8 mitotic figures in the 10 high-powered fields. Pituitary carcinomas are extremely rare tumors with cerebrospinal or extracranial metastasis.

Discussion
We take into account the possibility of ectopic secretion of IGF other than growth factors and/or factor causing sensitivity to IGF. However, this remains speculation. Therefore, we would like to present him hoping for help from the European Endocrinologists.

DOI: 10.1530/endoabs.3.P230

Endocrine Abstracts (2013) Vol 32
immunoreactivity 10%. Postoperative PRL level reduced to 65 ng/ml and no solid lesion was seen in postoperative imaging. His medical treatment is now ongoing.

Conclusion
Because of the atypical and ≥2 mitotic activity, necrosis in the nasal punch biopsy, also 38 HU solid lesion in tomography and absent of distant metastasis, we thought primarily atypical adenoma in this case. Although histopathological result is consistent with benign prolactinoma, it must be considered that its biological behavior may be progressed to malignancy after several years.

DOI: 10.1530/endoabs.32.P231

P232
Bilateral third nerve palsy secondary to an apoplexy in a pituitary macroadenoma causing Cushing’s disease: a very rare complication of a rare entity
Agata Juszczak, Claudia Worth, Niki Karavitaki & Ashley B Grossman
Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford University, Oxford, UK.

Introduction
Bilateral 3rd nerve palsy is known in conditions such as diabetes mellitus, neurocysticercosis, Guillain-Barre syndrome, multiple sclerosis, anterior or posterior communicating artery aneurysm or mesencephalic bleed/trauma. There are only single cases reported in association with pituitary adenoma or carcinoma, usually in the context of apoplexy. We describe a patient with Cushing’s disease and bilateral 3rd nerve palsy secondary to apoplexy in pituitary macroadenoma.

Case presentation
A 54-year-old man with background of ulcerative colitis, recent-onset hypertension, hypokalaemia and type 2 diabetes was referred to the gastroenterologist with weight loss. CT of the abdomen revealed bilateral adrenal enlargement and a random cortisol was elevated at 1800 nmol/l, and he was referred to the endocrine unit. The patient was admitted for further investigation: he had a severe proximal myopathy and peripheral oedema. His midnight sleeping cortisol was 3200 nmol/l (normal <50 nmol/l). As his ACTH was elevated at 188 ng/l, a MRI scan of the pituitary was arranged and showed a pituitary macroadenoma with left cavernous sinus invasion. The patient rapidly developed a left-sided 3rd nerve palsy, which was followed by confusion and then right 3rd nerve palsy 24 h later. His serum cortisol increased to 7500 nmol/l. A CT confirmed haemorrhage into the pituitary macroadenoma. The patient developed septicemia and associated thrombocytopenia and was not fit for transsphenoidal surgery. Four days following the apoplexy his 0900 h serum cortisol fell to 50 nmol/l. As his ACTH was elevated at 270 nmol/l and in view of his sepsis hydrocortisone replacement was added. Six weeks later patient remains hospitalised with persistent bilateral 3rd nerve palsy and is awaiting pituitary surgery after rehabilitation.

Conclusions
Bilateral 3rd nerve palsy, though very rare, can occur in Cushing’s disease, and if of acute onset is suggestive of pituitary tumour apoplexy. In this patient, the massive surge in serum cortisol was considered to be secondary to the pituitary apoplexy.

DOI: 10.1530/endoabs.32.P232

P233
Good response to temozolamide therapy in a man with a prolactin secreting pituitary carcinoma
Ismene Bilbao, Mariano Alvarez Coca, Cristina Garcia, Nerea Egan, Maite Aranburu, Alfredo Yoldi, Luisa Antunano & Miguel Goena
Hospital Universitario Donostia, San Sebastian, Spain.

Introduction
Pituitary carcinomas are rare and their management is difficult, because they exhibit a continued growth and metastatic dissemination despite of multimodal and aggressive treatments. Temozolamide, has shown a substantial response rates in pituitary carcinomas.

We report the case of a patient with a malignant prolactinoma successfully treated with temozolamide.

Case report
The patient, a 62-year-old male, consulted with severe headaches. He was diagnosed of a macroadenoma but due to poor response to cabergoline and persistence of the headaches, he underwent surgery in 2 occasions, and was treated with conventional radiotherapy and cabergoline which allowed control of prolactin, headaches and pituitary remant for a year. By the time that the headaches were back, the prolactin levels showed lack of response to cabergoline and bromocriptine treatment, and he developed hepatic, bronquial and vertebral metastasis. He was commenced of Temozolamide (200 mg/m², 5 days every 28 days) for 18 cycles and the prolactin levels responded dramatically, as well as the residual tumor size and the hepatic and bronquial metastasis. He received radiotherapy for the vertebral metastasis and is currently still receiving temozolamide. The treatment has been well tolerated.

Conclusion
Although pituitary carcinoma remains difficult to diagnose and manage, it seems that Temozolamide, an orally administered alkylating agent, may be an effective option for pituitary carcinomas.

DOI: 10.1530/endoabs.32.P233

P234
Combined choroidal neovascularization and hypopituitarism in a patient with homozygous mutation in methylenetetrahydrofolate reductase gene
Aydogan Aydogdu, Cem Haymana, Kamil Baskoy, Ali Hakan Duruhan, Gokhan Ozgur & Omer Azal
1Department of Endocrinology and Metabolism, Gulhane School of Medicine, Ankara, Turkey; 2Department of Endocrine and Metabolism, Gulhane School of Medicine, Ankara, Turkey.

Introduction
Hypopituitarism is defined as either partial or complete deficiency of anterior or posterior pituitary hormone secretion or both. Hypopituitarism itself may increase the risk of thromboembolism/hypercoagulopathy, and underlying mechanisms of hemostatic dysfunctions in hypopituitarism are mostly unknown. Reduced enzymatic activity due to methylenetetrahydrofolate reductase (MTHFR) gene mutations are associated with hyperhomocysteinemia and have been linked to both arterial and venous thrombosis. Choroidal neovascularization (CNV) in the macular area is one of the major causes of severe visual. Relationship between MTHFR and hypopituitarism in patients with Sheehan syndrome was also shown previously. Except for the Sheehan syndrome, any association of MTHFR mutation with hypopituitarism could not be identified to date.

Case report
We report a case of choroidal neovascularization (CNV) secondary to MTHFR gene mutation in a 20-year-old male patient with hypopituitarism. There was no history of pituitary surgery, radiotherapy, cranial trauma, pituitary apoplexy, subarachnoid hemorrhage or ischemic stroke. Finally, no primary cause of hypopituitarism could be found except a MTHFR gene mutation. Treatment with three consecutive injections of intravitreal ranibizumab (anti-vascular endothelial growth factor) resulted significant improvement of the patient’s vision and the appearance of the macula. With hormone replacement therapy of hypopituitarism, also acetyl salicylic acid 100 mg/day was started. The patient was clinically stable both for CNV and other thromboembolic disorders over a 1-year follow-up period.

Conclusion
CNV and hypopituitarism associated with a MTHFR gene mutation is highly unusual. Although there are no recommendations in this regard, the observations in the present patient indicate that antiangiogenic therapy can be useful and safe for the treatment of CNV in such a condition. Along with corticosteroids, levotroxin and testosterone replacement for the hypopituitarism, ASA treatment to prevent recurrent embolic events could be a reasonable approach when thrombotic ophthalmic complications occur in subjects with a MTHFR gene mutation.

DOI: 10.1530/endoabs.32.P234

P235
Acute pulmonary edema as the initial presentation of a pheochromocytoma: case report
Eduardo Resende, Maritza Sá, Margarida Ferreira & Silvestre Abreu
Department of Endocrinology, Hospital Central do Funchal, Funchal, Madeira, Portugal.

Introduction
The acute onset of pulmonary edema and severe congestive heart failure secondary to catecholamine overproduction from a pheochromocytoma is a rare
entity, especially in the absence of other signs or symptoms suspicious of this tumour. Myocardial involvement can include angina pectoris, acute heart failure, dilated cardiomyopathy, myocardial infarction and arrhythmias. Here, we present the case of a young man with no significant medical history who presented with acute pulmonary edema and dilated cardiomyopathy secondary to a unknown pheochromocytoma.

Case report
A 29-year-old caucasian male presented in the emergency room with an acute pulmonary edema, which resolved with minimal therapy; he had no cardiovascular risk factors (including hypertension), but he complained of palpitations and diaphoresis since 3 months ago. It was performed an echocardiogram which revealed a dilated cardiomyopathy with severe decline of systolic function. Twenty-four hour catecholamine and metanephrine levels were obtained: total metanephrine level of 6073 μg/24 h (normal value <1600), normetanephrine of 5197 μg/24 h (normal between 105 and 354), total catecholamine level of 1281 μg/24 h (217-575), noradrenaline of 958 μg/24 h (23–105). He was ordered an abdominal computed tomography, which revealed a 4.8 x 3.7 cm left adrenal mass. The patient was started on phenoxybenzamine (10 mg by mouth four times a day), and posteriorly with carvedilol (0.25 mg twice a day); 2 months later he underwent a laparoscopic left adrenalectomy with no complications. In the follow-up, it was verified a complete regression of the cardiomyopathy, with return to normal systolic function; he is currently doing well.

Discussion

Pheochromocytoma is a rare clinical entity and a diagnostic challenge, even more in this clinical setting; it should be included in the differential diagnosis of acute congestive heart failure when no other obvious cause can be elicited.

DOI: 10.1530/endoabs.32.P236

P237
Suppurative meningitis as a life threatening primary presentation of macroprolactinomas
Lina Akkache, Katia Daffeur, Nadia Kalafate, Meriem Haddad & Farida Chentli
Department of Endocrine and Metabolic Diseases, Bab Oued Hospital, Algiers, Algeria.

Introduction
Suppurative meningitis (SM) is a life threatening disease. It is rarely observed as a primary presentation in large pituitary tumours (PT) destroying the sellar floor and/or invading the skull base. Our aim is to report 3 SM revealing macroprolactinomas.

Case No. 1
A man aged 22, consulted for vomiting and fever. The diagnosis of SM was confirmed by lumbar puncture and blood cultures. Cerebral MRI showed multidirectional PT invading cavernous sinuses. Hormonal assessment demonstrated high prolactin with pituitary deficits (PD). After antibiotics SM was sterilized. Then, the PT was treated with dopamine agonists that were successful on prolactin and tumour size. The SM never relapsed, although the sellar floor was not surgically repaired.

Case No. 2
A male aged 49 hospitalized for the fourth bacterial SM episodes. Cerebral MRI showed an invasive and multi directional PT. The SM was cured by antibiotics. Prolactin was normalized by bromocriptine and the tumour size was significantly reduced. There was not any SM relapse.

Case No. 3
A man aged 25, with a history of arrested puberty, diagnosed as having a macroprolactinoma, with supra, infra and latero-sellar expansions revealed by a SM due to pneumococcal infection. The SM was sensitive to antibiotics, prolactin normalized under bromocriptine and tumour volume decreased progressively. There was not any relapsing.

Conclusion
Primary SM (PSM) rarely reveals PT, except if this one is very aggressive. To our knowledge only 52 cases have been reported. PSM can precede cerebrospinal leak which should be treated by surgery to avoid life threatening complications.

DOI: 10.1530/endoabs.32.P237

P238
Craniofacial fibrous dysplasia and pituitary gigantism in a 10-year-old boy; clinical case
Anna Gusova & Nadezhda Mazerkina
Scientific Research Institute of Neurosurgery n.a. N.N. Burdenko, Moscow, Russia.

Introduction
The combination of poly/monostotic fibrous dysplasia, café-au-lait pigmentation of the skin and endocrine hyperfunction (mostly precocious puberty) is known as McCune–Albright syndrome (MAS), a genetic origin syndrome with low incidence. The molecular basis of MAS is a mosaic activating mutation of the a subunit of the G protein (Goα) gene.

We present a clinical case of a 10-year-old boy with partial MAS and GH-secreting pituitary adenoma treated with octreotide-LAR.

Clinical case
The patient at the age of 5 years manifested headache and growth acceleration (10 cm per year). At 10 years, he was 176.6 cm tall. Examination revealed normal body proportions, normal body weight and height. At the age of 10 years, he was 176.6 cm tall. Examination revealed elevated serum GH (20 ng/ml, supression during OGTT minimum to 11.3 ng/ml), IGF1 (1176 ng/ml), IGF-BP3 (128 nmol/l) and prolactin (2480 IU/l). MRI found a pituitary microadenoma and CT showed signs of fibrous dysplasia of frontal, sphenoid and ethmoid bones. No café-au-lait spots or other endocrinepathy was observed. The therapy with octreotide-LAR and cabergoline was started. During 4 months of follow-up patient developed normal puberty and grew up on 27 cm. Lab test showed normalisation of prolactin (with no elevation during 2-year self-withdrawal period) and appearance of secondary hyperthyroidism. He receives octreotide-LAR 40 mg for at least 2 past years and cabergoline 0.25–1 mg per week. The decrease of IGF1 (to 700–800 ng/ml which is within the 95th percentile) and GH (minimum to 7.3 ng/ml) were observed. In 4 years of treatment, IGF1 level rose again to 1182 ng/ml. No CT and MR signs of tumor progression/reduction or deterioration of bone lesions were seen.

Conclusion
We report a clinical case of MAS in a child associated with GH-secreting adenoma treated conservatively with octreotide-LAR. The therapeutic response was insufficient and curative treatment was required. Despite there is a partial
MAS with few organ involvement, the specificity of endocrinopathy determines a burden of the disease.

DOI: 10.1530/endoabs.32.P238

**P239**

**Functional and transient effect of sodium excretion in combined pituitary failure with central and peripheral diabetes insipidus**

Ana Gomes¹, Ana Martins², João Martins³, ¹, Sonia Vale⁴, ² & Isabel Carmo⁴
¹Santa Maria’s Hospital, Lisbon, Portugal; ²Lisbon Medical School, Lisbon, Portugal.

Introduction
Central and Peripheral Diabetes Insipidus are both rare conditions. Combined they may result in serious hypernatremia and water deficit that may pose a therapeutic challenge.

Case report
MHBCR, a caucasian female aged 52, was admitted to the Endocrine Department because of serious hypernatremia. A previous diagnosis of pituitary failure and central diabetes insipidus was established 4 years before, after pituitary surgery for a non-secreting pituitary adenoma and was treated with hydrocortisone 20-5-5 mg/day, i-thyroxine 123 μg/day and desmopressin 60 μg/day po and 80 μg/day intranasal. Because of an acute psychiatric episode she was medicated with lithium 400 mg/day, 7 days before. On admission hypernatremia was found (153 mEq/l), with normal serum potassium and renal function. Urine output was 12 400 ml/day. Lithium was interrupted, fluid i.v. administration was increased up to 6000 ml/day (normal and hypotonic saline), desmopressin 4 μg i.v. 12/12 h, hydrochlorothiazide 50 mg/day and indometacin 400 mg/day were initiated. In the next few days, urine output decreased to 6–7 l, water balance was almost null, with normal urea, but serum sodium increased to 180 mEq/day. Desmopressin was increased up to 4 μg i.v. 4/4 h but was ineffective. Dialysis was begun at the seventh intra-hospital day with correction of serum sodium to 160 mEq/l in a single session. Furosemide 40 mg/day, i.v. further normalized serum sodium to 132 mEq/l in the next few days.

Discussion
Combined central and peripheral diabetes insipidus may result in serious life-threatening hypernatremia because of massive water loss. In this case both conditions were conventionally treated but despite no evidence of hemoconcentration, sodium further increased in a dramatic way, pointing to a specific sodium excretion defect. The most likely explanation is increased renin-angiotensin-aldosterone activity because of volume depletion with increased distal tubule reabsorption of sodium. This possibility is supported by the transient nature of the defect and the very good response to furosemide.

DOI: 10.1530/endoabs.32.P239

**P240**

**Management of resistant prolactinoma: case report**

Anna Gusova
Scientific Research Institute of Neurosurgery n.a. N.N. Burdenko, Moscow, Russia.

Introduction
Prolactinomas are the most common tumors among hormonally active pituitary adenomas. Therapy with dopamine agonists (DA) remains the first treatment choice. However there remain definite numbers of prolactinomas resistant to standard DA therapy. The underlying mechanisms of this phenomenon, management and prognosis are still poorly understood. The search of treatment options for overcoming DA-resistance is an important object in practical endocrinology. We present a clinical case of successful treatment of a man with partially DA resistance with co-administration of quinagolide and cabergolin.

Clinical case
A 58-year-old man presented slight visual impairment, headache and fatigueability. Magnetic resonance imaging (MRI) found an endo-infra-suprasellar pituitary adenoma. Laboratory examination revealed hyperprolactinemia (prolactin 4961 IU/l) and secondary hypogonadism. Administration of dopamine agonists (max dose of Cabergolin 5.5 mg per week) led to improvement of visual function and slight decrease of prolactin level (not normalization) with no effect on tumor size on MRI evidence. The decision to add Quinagolide (in max dose 150 μg daily) to therapy was made after 2.5 years of Cabergolin monotherapy. Cabergoline dose was slightly diminished. After 5 months of the combine therapy was observed normalization of prolactin and testosterone level.

Conclusion
This clinical case is an example of successful treatment of partially DA-resistant prolactinoma. The combination of different dopamine agonists allowed to overcome medication resistance and restore gonadal function.

DOI: 10.1530/endoabs.32.P240

**P241**

**Addisonian crisis: rapid correction of hyponatremia leads to osmotic myelinolysis**

Richard Parhimovich
Moscow Regional Research Clinical Institute, Moscow, Russia.

Chronic hypovolemic hyponatremia is typical for Addisonian crisis and may provoke brain edema but its rapid correction may lead to myelinolysis. We report 2 newly diagnosed cases of primary adrenal insufficiency (PAI) associated with severe hyponatremia which correction was complicated by osmotic myelinolysis.

Case 1
Twenty-four-year-old female was admitted with vomiting, sopor, shock. Serum sodium was 83, glucose 3.6 mmol/l. Serum cortisol 34 nmol/l and ACTH 307 pmol/l confirmed PAI. Hydrocortisone and saline were administered. Within 2 h – apnoe, mechanical ventilation began, then coma revealed. 3% saline infusion was added: 400 ml during 4 h giving sodium rise to 107 mmol/l. Saline infusion continued and within 24 h serum sodium was 117 mmol/l (37 mmol/l rise per day). Magnetic resonance imaging (MRI) didn’t reveal the reason for persisting coma. Diagnosis of central pontine myelinolysis was considered and was confirmed later by MRI. Patient dies after 18 months lasting coma.

Case 2
Fifty four years female was admitted with abdominal pain, vomiting, hypotension, hyperpigmentation. Serum sodium was 104, glucose 4.6 mmol/l, cortisol 190 mmol/l, plasma ACTH 246 pmol/l, renin 40 mg/ml. Saline infusion begins and additionally 450 ml 3% saline during 10 h was administered giving sodium rise to 116 mmol/l. Than saline was infused and to the next day sodium level was 122 mmol/l (increase – 18 mmol/l/24 h). After 3-4 days of compensation parkinsonian signs appeared. MRI revealed extrapontine myelinolysis.

After 5 months of treatment – full neurological recover.

These cases highlight the importance of careful correction of hyponatremia in PAI. Fatal pontine myelinolysis in case 1 developed due to overzealous correction of chronic hyponatremia without necessary control and not in line with current recommendation: possible rate of correction is 8 mmol/l during the first and 8–10 during second days and only at first hours 1–1.5 mmol/l per hour increase is possible.

DOI: 10.1530/endoabs.32.P241

**P242**

**Pituitary apoplexy after suppression test in a patient with Cushing’s disease due to macroadenoma**

Fatih Kuzu¹, ², Taner Bayraktaroglu¹, ², Ayfer Aitas Erdogan², Sevil Uygun Ilikhan², Muammar Bilici³, Sanser Gul¹ & Ozlem Tokgoz⁴
¹Division of Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine, Bulent Ecevit University, Zonguldak, Turkey; ²Department of Internal Medicine, Faculty of Medicine, Bulent Ecevit University, Zonguldak, Turkey; ³Department of Radiology, Faculty of Medicine, Bulent Ecevit University, Zonguldak, Turkey; ⁴Department of Neurosurgery, Faculty of Medicine, Bulent Ecevit University, Zonguldak, Turkey.

Endocrine Abstracts (2013) Vol 32
Cushing’s disease is not likely to be pituitary apoplexy or macroadenoma. We present a case of pituitary apoplexy after dexamethasone suppression test for Cushing’s disease due to macroadenoma.

Case report
A 30-year-old man complained of headache and closure of the left upper eyelid. Two years ago he had a headache, and was diagnosed with non-functional macroadenoma of pituitary. In follow, insoppressibly serum levels of cortisol with dexamethasone were detected with normal levels of ACTH. He complained with headache and ptosis in the left upper eyelid with sudden loss of vision in the left. Magnetic resonance imaging of the sella turcica showed definite pituitary apoplexy and macroadenoma. Hemorrhagic diathesis tests were normal. He was treated successfully by endoscopic endonasal transsphenoidal surgery within several hours after onset of pituitary apoplexy. His symptoms and signs were significantly improved.

He is followed by glucocorticoid replacement therapy with i-thyroxine and androgens.

Conclusions
Endocrine stimulation tests need to be careful in patients with pituitary macroadenoma, and should be assessed on a case-by-case basis. Pituitary apoplexy and macroadenoma in the present patient is not likely to be seen in Cushing’s disease.

DOI: 10.1530/endobs.32.P242

Osteoporotic fractures as manifestation of Cushing’s disease
Cláudia Nogueira1,2, Selma Souto1,2, João Quinaz1,2, Daniel Braga1,2, Eduardo Vinha1,2, Elisabete Rios1,2, Irene Bernardes1,2, Jossé Pereira1,2 & Davide Carvalho1,2
1Centro Hospitalar São João, Porto, Portugal; 2Faculty of Medicine, University of Porto, Porto, Portugal.

Introduction
Cushing’s syndrome (CS) is a well-known cause of bone loss and osteoporotic fractures, which may be the initial manifestation of the disease and may present 2 years before CS diagnosis. Trabecular bone is usually the most seriously affected, and vertebrae and ribs are the typical fracture locations.

Case report
A 37-year-old man with dyslipidemia and obesity was observed due to hypertension and osteoporotic fractures, which may be the initial manifestation of the disease and may present 2 years before CS diagnosis. Trabecular bone is usually the most seriously affected, and vertebrae and ribs are the typical fracture locations.

Case report
A 26-year-old male patient presented with moon face, purplish striae, localize the ACTH secreting tumor by conventional imaging methods because these tumors are often small in size. Here we present a case of ectopic ACTH dependent Cushing syndrome diagnosed with octreotide scan.

Case study
Thirty-year-old man was admitted to intensive care unit at regional hospital. On admission, he was unconscious, with convulsions, spasms and 3-day long history of headache as well as body temperature up to 41.5°C. The patient was transferred to the Department of Infectious Diseases, with the suspicion of neuroinfection. MRI findings suggested the presence of pituitary abscess and extensive pathological lesion with the size of 27×28×38 mm with intense marginal contrast enhancement, located in the sellar-suprasellar region. The lesion protruded into the sphenoid sinus through lowered Turkish saddle. Fluid content was also found in the sphenoid sinus. After 10 days of antibiotic therapy, the patient was transferred to neurosurgery ward for surgical treatment. Partial evacuation of pathological lesion was performed during frontotemporal craniotomy. Patient’s general condition following the surgery was moderately severe; the patient was conscious and able to react to simple instructions, he had left paresis affecting particularly left lower limb and he also experienced speech disturbances. Signs of hypopituitarism in all hormone axes were found and the patient was referred to the Department of Endocrinology at Pomeranian Medical University for further treatment. Follow-up MRI showed persistent pathologic mass in the sellar-suprasellar region, which penetrated sphenoid sinus through destroyed saddle floor. Once hormone deficiency has been corrected and the patient completed several weeks of antibiotic therapy, he was transferred to the Department of Neurosurgery at Pomeranian Medical University for further surgical treatment. Transsphenoidal resection of sellar-suprasellar tumour and sphenoïd sinuplasty were performed. Histopathologic findings confirmed the diagnosis of pituitary adenoma. The patient was referred to rehabilitation unit. One year later, check-up MRI showed deepened Turkish saddle filled with a mass corresponding to post-operative material. There was no evidence of recurrent proliferation process.

DOI: 10.1530/endobs.32.P244

Ectopic acth dependent Cushing syndrome diagnosed with octreotide scan
Eida Demir Önal1, Oguzhan Oguz1, Burçak Polat1, Zühal Kandemir2, Nurettin Karaölanoglu, Reyhan Ersöz1 & Bekir Çakır3
1Endocrinology and Metabolic Disease Department, Ankara Atatürk Education and Research Hospital, Yildirim Beyazit University Ankara, Turkey; 2Nuclear Medicine Department, Ankara Atatürk Education and Research Hospital, Yildirim Beyazit University Ankara, Turkey; 3Chest Surgery Department, Atatürk Chest Diseases and Chest Surgery Education and Research Hospital, Ankara, Turkey.

Ectopic secretion of corticotropin(ACTH) by nonpituitary tumors accounts for 10–15% of ACTH dependent Cushing’s syndrome(CS). Generally it is difficult to localize the ACTH secreting tumor by conventional imaging methods because these tumors are often small in size. Here we present a case of ectopic ACTH syndrome diagnosed with octreotide scan.

Case
A 26-year-old male patient presented with moon face, purplish striae, supraclavicular fat pads and proximal muscle weakness. In laboratory examination; early morning cortisol: 33 µg/dl (6.2–19.4), late evening serum cortisol: 30 µg/dl (2.3–11.9), serum potassium: 2.3 mmol/l (3.5–5.1), and urinary cortisol excretion: 258 µg/day (0–60). There was no cortisol suppression with low dose or high dose dexamethasone. As plasma ACTH concentration was 92 pg/ml (0–60) the patient was diagnosed with ACTH-dependent CS. Pituitary MRI revealed no mass. Inferior petrosal sinus sampling(BIPSS) was negative with no increase in ACTH after CRH administration. On thorax CT there was a 14 mm nodule in the middle lobe of the right lung. There was no pathology on 18-FDG-PET scan. But 111-In-Octreotide scan depicted the neuroendocrine tumor located in the right lung. In the lobectomy specimen the pathology of the mass was compatible with classic type carcinoid.

DOI: 10.1530/endobs.32.P243

Cerebrospinal meningitis in 30-year-old man as first manifestation of pituitary macroadenoma
Elżbieta Andrysiak-Mamos1, Leszek Sagan1, Elżbieta Sowińska-Przępierna1, Jakub Płobocki1, Agnieszka Kazmierczyk-Puchalska1, Małgorzata Zajac-Marczewska1, Ireneusz Kojder2 & Anhelli Syrenicz1
1Department of Endocrinology, Metabolic Diseases and Internal Diseases, Pomeranian Medical University, Szczecin, Poland; 2Department of Neurosurgery, Pomeranian Medical University, Szczecin, Poland; 3Department of Infectious Diseases, Pomeranian Medical University, Szczecin, Poland.

Introduction
The most frequent clinical manifestations of pituitary macroadenoma include headache, vision disturbances and cranial nerve paralysis.

Case study
He is followed by glucocorticoid replacement therapy with i-thyroxine and androgens.

Conclusions
Endocrine stimulation tests need to be careful in patients with pituitary macroadenoma, and should be assessed on a case-by-case basis. Pituitary apoplexy and macroadenoma in the present patient is not likely to be seen in Cushing’s disease.

DOI: 10.1530/endobs.32.P244
**P246**

**Thalassemia minor associated with multiple pituitary hormone deficiency**

Zsuzsanna Szántó, Imre Zoltán Kun, & Galafeleon Oltean

*1University of Medicine and Pharmacy, Targu Mures, Romania; 2 Clinic of Internal Medicine, Targu Mures, Romania.*

Regular red blood cell transfusions for thalassemia major leads to iron overload in endocrine glands, inducing deficient function of the pituitary, thyroid, parathyroid etc. In thalassemia intermedia these endocrine disturbances may appear due to increased intestinal iron absorption and occasional transfusions, but are less frequent and milder. We have no data about their presence in thalassemia minor. We present the case of a young woman known with mild hypochromic anemia since the age of 16. Her mother and brother have chronic anemia, too. She received iron therapy orally a few times, and parenterally 2–3 times, without the cause of anemic syndrome being clarified. She gave birth to a single child, and menstruations ceased at 29-years of age, after a prolonged psychological stress. Endocrine evaluation was performed after two years of secondary amenorrhea, the 31-years-old patient presenting also memory loss, constipation, cold intolerance, flushes of heat, asthenia, intermittent headache. Physical examination showed short stature, pale skin, rare sexual hair, RR: 80/60 mmHg, HR: 60 bpm. Laboratory detected low or subnormal level of pituitary and corresponding peripheral hormones (TSH: 0.48 mIU/ml, normal: 0.38–4.31; FT4: 0.35 ng/dl, normal: 0.82–1.63; LH: 6.6 mIU/ml, normal: 4.5–11; FSH: 1.8 mIU/ml, normal: 1.7–13.3; estradiol: 0.8 pg/ml, normal: 40.7–220.4, AM cortisol at baseline: 7.25 µg/dl, normal: 6.4–21, cortisol after long Synacthen-test: 39.59 µg/dl, normal: 41–28.9, anemia (Hb: 9.9 g/dl, HCT: 31.3%, MCV: 65.2L, MCH: 20.6 pg, Hgb electrophoresis: HbA1: 93.5%, HBF: 0.9%, HbA2: 5.6%). The pituitary CT-scan was normal. L-thyroxine (50mcg/day) and sexual hormone replacement therapy (2 mg/day estradiol for 21 days, and 2×100 mg/day progesterone for 10 days) were started, followed by artificial menstrual cycles, without aggravation of the anemic syndrome. Mild hyperprolacemia (PRL: 56.5 ng/ml) with galactorrhea appeared, and the dose of estradiol was reduced to 1.5 mg/day, the clinical and laboratory status being under control now. We discuss the possible explanations of the association between two rare diseases: thalassemia minor and pituitary failure of apparently non-organic etiology.

**Endocrine Abstracts (2013) Vol 32**

**P247**

**Occurrence of De Quervain’s thyroiditis after resolution of hypercortisolism following SOM230 treatment for Cushing’s disease and surgery for an adrenocortical adenoma: report of two cases**

Zoe Efstathioudou, Albana Sykja, Panagiotis Anagnostis, Athanasios Panagiotou & Marina Kita

*Department of Endocrinology, ‘Hippokration’ General Hospital of Thessaloniki, Thessaloniki, Greece.*

**Introduction**

Increased prevalence of thyroid autoimmunity has been described in few cases after successful treatment for Cushing’s syndrome. In De Quervain’s thyroiditis (DQT) autoimmune it does not seem to play a primary pathogenetic role. We describe two cases of DQT coinciding with the resolution of hypercortisolism, after successful treatment of Cushing’s syndrome/disease.

**Case 1**

A 41-year-old female with Cushing’s disease who refused neurosurgery was started on SOM230. On the third month of successful treatment (URC = <4 µg/24 h), she experienced a febrile state accompanied by malaise and severe neck pain. Clinically, thyroid was tender at palpation and tachycardia was noted. Laboratory tests revealed thyrotoxicosis (TSH = 0.065 mU/l, FT4 = 2 ng/dl, and elevated ESR (110 mm/h). Thyroid uptake was absent on a technetium thyroid scan and thyroid ultrasonography was indicative of DQT. SOM 230 was temporarily discontinued, but due to persistence of fever and pain, despite non-steroidal anti-inflammatory medication, glucocorticoid treatment with methylprednisolone was initiated, resulting to a dramatic clinical improvement.

**Case 2**

A 50-year-old female patient with Cushing’s syndrome due to a cortisol secreting adenoma had undergone unilateral adrenalectomy and been placed on glucocorticoid substitution due to HPA axis suppression. Five months post-operatively, at an attempt to taper hydrocortisone dose, she developed left sided neck pain, radiating to jaw and ear, accompanied by low grade fever and malaise. Laboratory tests showed thyrotoxicosis, high ESR and negative thyroid auto-antibodies. Thyroid ultrasonography and scintigraphy confirmed the diagnosis of DQT. She was treated with prednisolone resulting in immediate symptomatic relief.

**Conclusions**

The incidence of DQT upon successful therapy of hypercortisolism, either medical or surgical has raised the question of its pathogenetic mechanism could only be speculated. Perhaps the relative or absolute glucocorticoid deficiency, after effective treatment of hypercortisolism, alters immunologic responses and renders patients more vulnerable to thyroidic processes.

**DOI:** 10.1530/endoabs.32.P247

**P248**

**Nephrogenic systemic fibrosis: potential aetiology of pituitary stalk thickening post-commencement of dialysis: case report**

Sajini Wijetilleka & Chantal Kong

*1Watford General Hospital, Watford, UK; 2 St Albans City Hospital, St Albans, UK.*

Non-neoplastic pituitary stalk thickening is rare in patients without life-threatening disorders and diabetes insipidus. We present a non-diabetic patient with end stage renal failure with hyperprolactinaemia and pituitary stalk thickening. A 53-year-old Nigerian gentleman presented with reduced libido, erectile dysfunction and painful gynaecomastia. He denied galactorrhea, headaches or visual disturbances. He previously received spironolactone for resistant hypertension and soon commenced dialysis for his end-stage renal failure investigations showed low testosterone level of 6.3 and elevated prolactin levels of 2683 which was attributed to hypogonadism secondary to ESRF. Serum oestradiol was 48, FSH 9.2, and LH 0.9. MRI pituitary in 2009 showed an expansion in the pituitary stalk measuring 5 mm with minimal mixed signal. He was commenced on Bromocriptine which normalised his prolactin. He improved symptomatically, though his gynaecomastia persisted. In 2012, the patient stopped Bromocriptine due to nausea. He commenced of cabergoline and testim gel. A repeat MRI in 2012 showed no interval change despite the commencement of dopamine agonist.

Subsequent review of pre-dialysis MR renal imaging showed a small left kidney with an absence of renal artery stenosis. Investigations to determine the aetiology of his hypertension showed an elevated standing aldosterone/renin ratio of 2181 with normal adrenals on CT imaging; rendering his hypertension as essential. Recent literature notes that patients in dialysis-dependent kidney failure are at significant risk for a recently described scleroderma-like disorder called nephrogenic systemic fibrosis. Nephrogenic systemic fibrosis (NSF) is associated with dermopathy and multi-organ dysfunction. No prior reports note pituitary involvement. Gadolinium-based contrast agents have been implicated in the development of nephrogenic systemic fibrosis. Our patient had an elevated prolactin before receiving gadolinium for his MR Renal Angiogram prior to commencing dialysis. We hypothesise his pituitary stalk thickening, which did not change post-bromocriptine is secondary to NSF.

**DOI:** 10.1530/endoabs.32.P248
Our case report will show that paranganglioma can be an ‘actor’ of clinical hydrogenase subunits B and D), which has not been confirmed. Comprehensive slightly in the surgical bed in left periaortic field. At the same time by the NIH the salivary glands, lungs, liver, gastrointestinal tract and urinary bladder, without University, Budapest, Hungary.

The presence of pheochromocytoma/paranglioma can be characterized by typical clinical signs, due to hemodynamic and metabolic activity of circulating catecholamines or less a consequence of other amines or neuropeptides produced simultaneously. But the clinical picture can be also very different and can play a clinical picture of other diseases. The authors present a case report from a patient with retroperitoneal paranglioma. The patient was admitted to our unit because of high blood pressure, hyperglycemia and weight loss. The reason for the CT was differential diagnosis of cachexy. CT found a solid body left paraaortal retroperitoneal tumor (size 8.5 x 4.5 x 5.5 cm), which was consistent on the aorta and renal artery and had necrotic disintegration. The patient subsequently passed the examination of adrenal scintigraphy with 131I-MIBG, which described paranglioma left paraaortal, radiopharmaceutical uptake was present in both adrenals and one lymphatic nodule in mediastine – the possibility of exclusion metastatic malignant pheochromocytoma. We performed PET-scan, with the picture of present bearing signs of central necrosis in the retroperitoneum (left paraaortal) with only a low 18-FDG metabolism, and no other pathological changes in relation to the underlying disease on PET/CT image. To exclude MEN 2A syndrome we examined parameters of the thyroid gland (also with USG control), where we found the presence of cystic bearing (size 7.6 x 11.5 mm). Puncture aspiration biopsy of the node showed adenomatous node with cystic changes. The patient underwent genetic testing, which excluded RET mutation-protooncogen. The patient was subsequently operated at Urology Department, the tumor was extirpated and the histological examination showed that this was a retroperitoneal extra-adrenal paranglioma (with angi invasion, perineural spread, and extension into fat) with a recommendation to continue to monitor the patient. To assess the residual findings we performed PET scan, which described pathological heterogeneous tissue with increased metabolic activity in the retroperitoneum in place of the original tumor. The patient was without clear symptoms of the underlying disease activity in PET/CT image of 18-FDG. The laboratory results as well as the PET results, we consulted with professor Karel Pacak, from NIH (National Institute of Health), Bethesda, MD, USA, in order to exclude a possible recurrence. The patient was hospitalized in NIH and passed through this hospitalization complete biochemical and imaging studies. Scintigraphy with 123I-MIBG showed a normal distribution of MIBG activity in the salivary glands, lungs, liver, gastrointestinal tract and urinary bladder, without evidence neuroendocrine tumor FDG/PET radiopharmaceutical recaptured only slightly in the surgical bed in left periarteric field. At the same time by the NIH genetics the patient was tested for familial paranglioma (mutation succinate-dehydrogenase subunits B and D), which has not been confirmed. Comprehensive examination of disease recurrence was ruled out for now. Our case report will show that paranglioma can be an ‘actor’ of clinical picture. In the diagnostic process is today also genetic examination very necessary, because of the knowledge of new gene mutations in the pathogenesis of endocrine diseases.

Introduction

Malignant schwannoma in a patient with hypopituitarism, congenital hydrocephalus, atraial septal defect and agenesia of right kidney

Ljiljana Marina, Svetlana Vujovic, Marija Barac, Miorina Ivovic, Milena Tantic-Gajic, Zoran Arizanovic & Dragon Micic

Clinic for Endocrinology, Diabetes and Metabolic Diseases, Belgrade, Serbia.

Introduction

Schwannomas are tumors derived from myelin sheat of nerves which can displace and compress nerves causing pain, weakness and numbness. Very rarely they become malignant.

Case report

Thirty-one years old patient was hospitalized at our Department to evaluate hypopituitarism. He was born at term by cesarean section, with hydrocephalus and did not start to breath spontaneously. A few months later, he was diagnosed with scoliosis thoracalis duplex and ostium secundum atrial septal defect. Hydrocephalus spontaneously resolved at the age of four and at the age of five he was diagnosed with hypopituitarism – GH deficiency, hypogonadotropism, hypothyroidism and hypoadrenalinism. Endocrinological testing showed adequate cortical response in ACTH test and insulin tolerance test. At the age of nine due to congenital spinal curves he underwent a surgery but significant spine gibus remained. At ten, he was diagnosed with Asthma bronchiale and congenital heart defect was surgically treated. From 11th to 16th year of age while on GH replacement therapy he grew from 92 to 154 cm. At the age of 12, a CT scan of the head was performed: Empty sella and a CT scan of the abdomen: agenesis of the right kidney. At the age of 27, due to a constant pain in his left shoulder and MRI was performed. It showed a tumefaction of 15 mm oval-shaped nodule, with solid density (43 HU) on the left adrenal gland, pitiutary MRI was suggestive for a 3 mm microadenoma, and cortisolemia was high (1.083 nmol/l, n: 171–536), besides high ACTH (452.2 pg/ml, n: 7.2–63.3) and 17-OH progesterone (129 ng/ml, n: <1.39) level, that rose the suspicion of an ACTH-producing adenoma. The possible causes of these changes are discussed.

Conclusion

This case represents a very rare evolution of classical CAH that after 17 years of proper glucocorticoid therapy complicates with a left adrenal tumor and a pituitary microadenoma.

DOI: 10.1530/endoabs.32.P250
P252
Non-Hodgkin's lymphoma presenting as anterior hypopituitarism
Shang Ming Samuel Lee1,2, Chen Weiiliang Abel1,2, Cher Liu1,2, Yuan Gabriel1,2, Wei Feng Lee1,2, Cheng Jye Seow1 & YC Kon1
1Tan Tock Seng Hospital, Singapore, Singapore; 2Ministry of Health Holdings, Singapore, Singapore.

Introduction
Panhypopituitarism is a known but rare presentation of lymphoproliferative disease. We describe a patient with newly diagnosed advanced diffuse large B-cell lymphoma who presented with anterior hypopituitarism and concomitant adrenal gland involvement.

Case report
A 72 year-old Chinese woman presented with a few weeks’ duration of lethargy, weight loss and functional decline. A hormonal screen done at admission suggested central hypothyroidism, and an MRI of the brain performed showed pituitary stalk thickening without abnormalities in the size and morphology of the gland. Evaluation of the other hormonal axes revealed the presence of central hypocortisolism, secondary hypogonadism and low IGF1 levels. In addition, a computed tomography scan done as part of work-up for a right hilar mass seen on a screening chest radiograph revealed bilateral adrenal masses with surrounding enlarged para-aortic lymph nodes. Histology of the adrenals was diagnostic of a diffuse large B-cell lymphoma and a work-up for other causes was inconclusive. Our patient was not subjected to a pituitary biopsy as there was sufficient evidence of lymphomatous infiltration of the gland from the clinical findings. She was started on six cycles of R-CHOP chemotherapy along with thyroxine and substitutive therapy. With the completion of chemotherapy, there has not been any functional recovery of the hormonal axes and our patient is currently still receiving hormonal replacement.

Conclusion
Panhypopituitarism is a rare but important aetiological consideration in the older patient presenting with functional decline. Our patient’s presentation of isolated anterior hypopituitarism was unusual, as secondary lymphomatous involvement has a tendency to affect the posterior lobe instead due to its direct blood supply from the systemic circulation, unlike in the anterior lobe.

DOI: 10.1530/endoabs.32.P252

P254
Recurrent pituitary tumor: the importance of a functional classification at diagnosis
Carolina Menezes, Isabel Paiva, Leonor Gomes, Luisa Ruas, Sofia Gouveia, Joana Saraiva, Daniela Guelho, Manuela Carvalheiro & Francisco Carrilho
Department of Endocrinology, Diabetes and Metabolism, University Hospital of Coimbra, Coimbra, Portugal.

Introduction
Pituitary tumors can be classified according to their endocrine function, starting from the clinical phenotype to establish a diagnosis. The histological analysis can confirm the clinical suspicion. A thorough classification is essential in the therapeutic approach with an important influence in the disease-free survival.

Case report
We report a case of a 16-year-old male, with loss of visual acuity and headache, attended by an Ophthalmologist in May/1993 who detected papilledema and suggested a CT that showed a sellar tumor with 4×2.8 cm. He was subjected to surgery in December/1993. Histological diagnosis was ‘non-functioning pituitary tumor’.

The post-surgical evaluation showed delayed puberty ( TannerPIG1) and bitemporal hemianopsy. Laboratory findings: deficit in the thyroid, gonadals, adrenal axis and diabetes insipidus, with normal GH. IGF1 and prolactin. MRI showed ‘intra and infra sellar tumor residue’. He was started on substitution therapy.

Beginning in late 1995, prolactin progressively rose to 152 ng/ml (n < 18 ng/ml), whereby in 1996 the patient was started on bromocriptine 2.5 mg, b.i.d. In 2000 was detected GH = 7.0 mIU/L (n < 4.3 mIU/L) with IGF1 = 377 ng/ml (n = 182-780 ng/ml), a 15 cm stature growth, without acromegaly symptoms or dysmorphism. Revision of the histological analysis: ‘Prolactin secreting pituitary tumor’

Persistently high random GH= 5.09 ng/ml (n < 4 ng/ml) and the elevation of IGF1 = 502 ng/ml (n = 117–319 ng/ml), motivated the initiation of somatostatin analogues in 2005. There was a favorable laboratorial response: GH = 3.41 ng/ml (n < 4 ng/ml), IGF1 = 292 ng/ml (n = 117–329 ng/ml) with reduction of the tumor residue dimensions.

At the present time, the patient has 34-years-old, a reasonable QoL under substitutive therapy, bromocriptine 10 mg, q.d., lamiretude 120 mg, every 6 weeks. The hormonal secretion is controlled: GH = 1.3 ng/ml (n < 1.0 ng/ml), IGF1 = 334 ng/ml (n = 115-307 ng/ml), prolactin = 10 ng/ml (n < 18 ng/ml), but the latest MRI performed in 2012 showed a tumoral residue of similar dimensions. He was proposed for radiation therapy.

Conclusion
This case illustrates the difficulties in the characterization of some pituitary tumors (either clinical, functional and pathohistological classification), specially in younger patients. The appreciation of the hormone levels must be integrated, considering the pubertal staging and not only chronological age.

DOI: 10.1530/endoabs.32.P254

P255
Congenital trans-sphenoidal meningocele: an uncommon cause of pituitary insufficiency
Faiza Belhimer, Abderrahim Bey & Farida Chentli
Department of Endocrinology and Metabolism, Bab El Oued Hospital, Algiers, Algeria.

Introduction
Congenital trans-sphenoidal meningocele (TM) is a rare clinical entity. It can be traumatic, congenital or from tumour origin. It results from a defect in the sphenoid bone ontogenesis. In its classical form, the TM is positive in adults, frequently in women in the fourth or fifth decade by rhinorrhea or cerebrospinal fluid leak through a bony defect in the sphenoid floor. Our aim is to report a case of large TM without rhinorrhea, and as a part of midline abnormalities.

Case report
An adolescent girl aged 19, was sent to our department for diabetes insipidus. Her medical history showed that she was treated since the age of four for growth retardation related to an isolated GH deficiency, but without any cerebral exploration. At 18 she complained from polyuria and polydipsia. Clinical and
paraclinical examinations argued for diabetes insipidus with well proved GH deficiency. Other pituitary functions were preserved. Cerebral MRI described a large dehiscence of the sellar floor with passage of cerebrospinal fluid through the sphenoidal sinus and persistence of meningeval wall defining a transphenoidal meningocele which appears to be a part of the midline abnormalities as it is associated to cleft lip and hypertelorism. Unlike other cases reported in the literature, our patient does not have rhinorrhea which represents a high risk for meningitis which is a life threatening condition for patients with this congenital malformation.

Conclusion
Congenital transsphenoidal meningocele is a rare condition, but should be kept in mind as a part of midline abnormalities and as a cause of pituitary insufficiency, cerebrospinal fluid leak and meningitis.

DOI: 10.1530/endoabs.32.P255

P256
Isolated ACTH deficiency with Brugada syndrome: a combination increasing the risk of fatal arrhythmia
Naoko Kumagai1, Kazufumi Honda1,2, Yohei Muroya1,2, Masanori Shimodaira1,2, Ken-ichi Yatsuzawa1,2, Erisa Soritamachi1,2, Akira Inamura1 & Keita Ishii1
1Moriya Keiyu Hospital, Ibaraki, Japan; 2Tokyo Metropolitan Hiro-o Hospital, Tokyo, Japan.

Introduction
Brugade syndrome (BS) is a cardiac disorder characterized by typical electrocardiograph (ECG) alterations and is known to have a high risk of sudden cardiac death (SCD). Isolated ACTH deficiency (IAD) is often associated with fetal arrhythmia. Previous reports have suggested that certain endocrine diseases might cause Brugada-like ECG forms. We present a case of IAD with BS who died suddenly.

Case presentation
Forty-one year-old man was referred to our department because of severe hypoglycemia in July 2011. An arrhythmia was pointed out at his annual medical checkup in 2010 and he was diagnosed as having BS by cardiologists. The hypoglycemia was confirmed in July 2011. A hyperpigmentation was found during his dermatological investigation. After the replacement therapy with hydrocortisone was started the patient had no symptoms of hypoglycemia. After his second ablation, he lost consciousness and died suddenly.

Discussion
BS is based on genetic defect concerning cardiac ion channels. On the other hand, several reports indicate that changes of thyroid hormone and cortisol and/or hyponatremia caused by adrenal insufficiency could induce Brugada-like ECG forms through the functional disorders in cardiac ion channels. In addition, abnormalities of ion channel function have been found in some patients with Schmidt syndrome. These reports suggest that IAD could influence in cardiac ion channel function in this case, though the detail of functional connection between these hormone and myocardinial ion channels remains unclear in humans.

Conclusion
This case shows us possibility that IAD can increase risk of fatal arrhythmia through its actions to cardiac ion channels.

DOI: 10.1530/endoabs.32.P256

P257
A case of primary adrenal failure diagnosed in postpartum period
İnan Anafıroğlu, Mustafa Köse & Ekrem Algın
Department of Endocrinology and Metabolism, Trabzon Kanuni Education and Research Hospital, Trabzon, Turkey.

Introduction
The prevalence of primary adrenal insufficiency (Addison disease; AD) in pregnancy is unknown. Female patients with adrenal insufficiency are usually infertile and once get pregnant are at increased risk for preterm deliveries, Cesarean section and babies with low birth weights. Recognition of AD during pregnancy may be difficult as many of the clinical complaints like weakness, lightheadness, syncope, nausea, vomiting, hypotension, and increased pigmentation can also be found in normal pregnancies. Herein, we present a woman with AD recognized at postpartum period.

Case report
A 32-year-old woman admitted with the complaint of hyperpigmentation throughout her body. She has given birth a healthy -2670 gr boy- at 36 weeks of gestation by vaginal delivery about 10 weeks ago before admission. The hyperpigmentation had started at the second trimester. She had no nausea and vomiting during gestation except the first trimester. At physical examination, there was generalized hyperpigmentation of the skin and knuckles, toes, elbows, knees, palms creases, nail beds, nipples, buccal mucosa and gums. She had a blood pressure of 105/70 mmHg and serum sodium, potassium, chloride and glucose were found to be at normal ranges. Morning serum cortisol was 5.73 ng/dl with a plasma ACTH of 1250 pg/ml. She did not respond to insulin-hypoglycemia test. Bilateral adrenal enlargement was present on abdominal CT examination. A diagnosis of AD was made and she was started on hydrocortisone therapy. It has been proposed that fetal cortisol production may be protective for the mother from severe adrenal insufficiency until the postpartum period. This may explain why our patient did not suffer an adrenal crisis during pregnancy.

Exacerbation of autoimmunity in the postpartum period may be another explanation for our patient.

Conclusion
Patients with subclinical adrenal insufficiency at early stages of the AD may present with a rather normal blood pressure and laboratory testing; so hyperpigmentation may be the only symptom in the patient.

DOI: 10.1530/endoabs.32.P258

P258
TSH secreting pituitary adenoma: a case report
Feyza Yener Ozturk, R Selvinaz Erol, Idris Kuzu, M Masum Canat, Savas Karatas & Yuksel Altuntas
Department of Endocrinology and Metabolism, Sisli Etfal Training and Research Hospital, Istanbul, Turkey.

Introduction
Thyrotropin secreting pituitary adenomas are rare constituting <2% of pituitary adenomas. Thirty percent of these tumors may be plurihormonal. Most common cosecreted hormone is GH and the least one is PRL. We report here a case of plurihormonal pituitary adenoma symptomatic for TSH secretion.

Case report
A 35-year-old female admitted to hospital because of fatigue, heat intolerance, headache, galactorrhea and menstrual irregularity. Her laboratory analysis showed hyperprolactinemia (PRL: 74 ng/ml), and high fT3 level with inappropriately normal TSH (TSH: 3.14 μIU/ml (n: 0.27–4.2 μIU/ml); fT3: 4.67 pg/ml (n: 1.96–4.36); fT4: 1.24 ng/ml (n: 0.72–1.56 ng/dl). GH level was also high but IGF1 levels were all normal and she did not have any signs or symptoms of acromegaly. Pituitary MRI showed 18×15 mm macroadenoma extending to suprasellar region. She was followed-up with cabergolin for a year. Then she had transsphenoidal hypophysectomy. The immunohistochemical staining showed that tumor cells were strongly reactive to GH, PRL and TSH; Ki67 index was 2%. Four months after operation, she got pregnant. There was no biochemical abnormality during pregnancy. Her pituitary MRI didn’t show any residual image. But at postpartum 2 months, high fT3 and fT4 levels were revealed. PRL was 60 ng/dl (analysis was done 4 h after breastfeeding); fT3: 4.39 pg/ml; fT4: 1.66 μg/dl; TSH: 23.33 μIU/ml; GH: 2.10 ng/ml; IGF1: 205 ng/ml (n: 109–284), cortisol was suppressed after dexamethasone suppression test (1.97 μg/dl). Physical examination revealed only tachycardia. Thyroid autoantibodies were all negative. Thyroid USG was normal other than a 5.3 mm heterogenous, isoechoic nodule. SHBG, glycoprotein alpha subunit to TSH ratio was also high but IGF1 levels were all normal and she did not have any signs or symptoms of acromegaly. Pituitary MRI showed 15×12 mm extending to optic chiasm, invading bilateral cavernous sinuses was found on MRI. Visual field was normal. Octreotide LAR 20 mg/month and propranolol 40 mg/day were started and reoperation has been planned.

Conclusion
This case emphasizes that all pituitary adenomas should be screened for secretion of all hormones and immunohistochemical staining of all pituitary hormones is mandatory for correct classification.

DOI: 10.1530/endoabs.32.P258
P259
Gastrointestinal bleeding associated with Dabigatran in a patient with panhypopituitarism
Fahri Gunes, Mehmet Asik, Hacer Sen, Emine Binnetoglu, Erdem Akbal, Ogun Irem Bilen, Kubilay Ukinc & Guzhan Adam
School of Medicine, Çanakkale Onsekiz Mart University, Çanakkale, Turkey.

Introduction
Dabigatran is a direct thrombin inhibitor which is used for reducing the risk of stroke or systemic embolism in patients with atrial fibrillation. Although INR monitoring is not required in the course of treatment, it may be complicated with spontaneous systemic bleeding. Sheehan’s syndrome is characterized with panhypopituitarism which is caused by necrosis of the pituitary gland. Recent studies have demonstrated that panhypopituitarism is associated with bleeding disorder.

In the current study, we report a case with panhypopituitarism who suffered from gastrointestinal bleeding while using dabigatran.

Case report
A 74-year-old female patient admitted to the emergency department with the complaint of weakness and melena for the last 3 days. The physical examination revealed hypotension and tachycardia. The patient has been treated with dabigatran for paroxysmal atrial fibrillation for the last 1 month. She had no history of previous bleeding and antiplatelet treatment.

The laboratory test results were consistent with severe anemia (Hb: 3.8 g/dl), elongation of prothrombin time (15.1 s) and INR (1.37). Upper gastrointestinal endoscopy revealed multiple erosions in antrum. The patient developed profound hypotension (Na: 119 mEq/l) and progressive lethargy on the third day of follow-up. The advanced examination showed adrenal insufficiency and central hypothyroidism.

Discussion
The Sheehan syndrome has a very large spectrum of clinical presentation ranging from non-specific symptoms to coma. It may also lead to bleeding tendency rarely. Clinicians should consider this rare complication especially in patients who are to be treated with dabigatran.

DOI: 10.1530/endoabs.32.P259

P260
Therapeutic dilemmas in a young male patient with macroprolactinoma complicated by hypogonadism
Wei Feng Lee, Liu Yuan Gabriel Cher, Shang Ming Samuel Lee, Weiliang Abel Chen, Cheng Jye Seow & Wai Han Ho
Tan Tock Seng Hospital, Singapore, Singapore.

Introduction
Hyponadism is known to persist after treatment of hyperprolactinemia, necessitating androgen therapy in young male patients. Aromatisation of testosterone to estradiol can result in tumor expansion. We report a patient with persistent hypogonadism post treatment of macroprolactinoma and discuss challenges involved in the management.

Case report
A 51-year-old gentleman was admitted for streptococcal meningitis. Brain imaging revealed a pituitary macroadenoma with invasion into the cavernous sinus and erosion into the sphenoid sinus resulting in persistent cerebrospinal fluid (CSF) rhinorrhea. Laboratory investigations: FSH <1 IU/l (RI 1–19), LH <1 IU/l (RI 1–19), Total Testosterone <1 nmol/l (RI 5–30), free T, 14 nmol/l (RI 5–21), TSH 0.51 mIU/l (RI 0.34–5.6), Prolactin 12,867 mIU/l (RI 77–274), Short synacthen test response (293±848±977 nmol/l). He underwent transtuboreal removal of the prolactinoma and post operatively was complicated by panhypopituitarism requiring thyroxine and hydrocortisone replacement. A weekly dose of 2.5 mg of Cabergoline was needed to normalise prolactin levels. He reported low mood, libido and erectile dysfunction post surgery. FSH, LH and testosterone remained undetectable. He was started on i.m. testosterone at 100 mg every 4 weeks with normalisation of testosterone levels to 26 nmol/l and resolution of hyperprolactinoma symptoms. His prolactin levels, expectedly, increased to 343 mIU/l. There were no signs and symptoms of raised intracranial pressure or cavernous sinus syndrome.

Discussion
Hyperprolactinemia supresses the pulsatile secretion of GnRH resulting in hypogonadism. Estrogen, from aromatisation of testosterone, stimulates prolactin secretion by stimulating prolactin gene transcription and disrupting the inhibitory influence of dopamine. We discuss benefits and problems of various management options should there be tumor expansion post initiation of testosterone. These include increasing the dose of cabergoline or the addition of an aromatase inhibitor. Regular prolactin measurements and imaging of the pituitary are needed.

DOI: 10.1530/endoabs.32.P260

P261
Baraitser–Winter’s syndrome and GH deficiency
Hadjer Zellagui & Farida Chentli
Department of Endocrine and Metabolic Diseases, Bab Oued Hospital, Algiers, Algeria.

Introduction
Baraitser–Winter syndrome (BWS) is a rare brain malformation leading to droopy eyelids and intellectual disabilities. This syndrome, first reported in 1988, is probably due to genetic abnormalities that are still not well defined, although eight gene abnormalities are already discovered and de novo missense changes in the cytoplasmic act-encoding genes ACTB and ACTG1 have been recently discovered (Rivièrre Nature Genetic 2012). The syndrome combines iris coloboma, bilateral ptosis, hyper 1etelorism, broad nasal bridge, prominent epicantic folds, brain malformations, and growth and mental retardation. To our best knowledge only 20 cases have been reported so far, among them five from Arab origin. Our aim is to describe the sixth Arab child with a phenotype that looks like Baraitser–Winter’s syndrome.

Case report
A girl aged 7 years old of consanguineous parents was referred for short stature and mental retardation. Clinical examination showed dwarfism and a delay in mental development. Other clinical features included: strabism, epicantid folds, broad nasal bridge, and brain anomalies such as lissencephaly, bilateral hygroma and cerebral atrophy. Hormonal exploration showed partial GH deficiency without other endocrine disorders.

Conclusion
Our case looks exactly like SWS. But, apart from facial and cerebral abnormalities, there is a partial GH deficiency which can explain the harmonious short stature. This case seems worth to be reported as it adds another abnormality to this very rare syndrome.

DOI: 10.1530/endoabs.32.P261

P262
Beer potomania masquerading as adrenal insufficiency
Louise Hopkins, Victoria Stokes & Sudesna Chatterjee
Stoke Mandeville Hospital, Aylesbury, UK.

A 71-year-old male ex-publican presented to the Medical Emergency Unit suffering from lethargy, weight loss, dizziness on standing and dyspnoea on exertion. He had a past medical history of hypertension, weight loss, dizziness on standing and dyspnoea on exertion. He had a past medical history of hypertension, ischaemic heart disease and alcoholic liver disease and he admitted to drinking 100 units of beer per week. His anihypertensive medications included lisinopril and hydrochlorothiazide. On examination BMI was 35 kg/m 2, blood pressure 85/65 mmHg and there was no buccal or palmar hyperpigmentation. Admission venous blood tests revealed glucose 2.8 mmol/l and sodium 113 mmol/l. This led to a working diagnosis of Addison’s disease. An MRI head, short synacthen test, ACTH and other baseline pituitary function tests were organised. MRI head revealed a structurally normal pituitary gland. The short synacthen test showed a low baseline cortisol of 109 nmol/l which rose to 510 nmol/l after 30 min. ACTH was 14 ng/l. All other tests were normal. Lisinopril and hydrochlorothiazide were stopped and he was commenced on i.v. hydrocortisone. This led to resolution of his hypotension and hyponatraemia. He was given a diagnosis of possible ACTH deficiency and discharged on replacement dose hydrocortisone to be followed up in the endocrine clinic. A repeat short synacthen test 3 months later showed a normal baseline cortisol of 513 nmol/l rising to 588 nmol/l after 30 min. Hydrocortisone...
therapy was stopped and hyponatraemia improved with changes to his antihypertensives and a reduced alcohol intake. The cause of the patient’s initial presentation was a combination of beer potomania and thiazide diuretic use. Beer potomania is an under-recognised condition characterised by hyponatraemia, secondary to water intoxication. Recognition of this condition and careful fluid administration are required in the initial phase to avoid serious complications such as central pontine myelinolysis. Our case demonstrates that other causes of euvoalaemic hypotonic hyponatraemia may obscure the actual diagnosis of beer potomania resulting in incorrect management.

DOI: 10.1530/endoabs.32.P262

P263
Isolated ACTH deficiency associated with Hashimoto’s disease
Emine Binnetoğlu, Mehmet Aşık, Hacer Şen, Fahri Güneş, Erdem Akbal, Zeliha Tekeli, Bettül Kızıldag & Kubilay Uknife
1Department of Internal Medicine, Medical Faculty, Çanakkale Onsekiz Mart University, Çanakkale, Turkey; 2Department of Radiology, Medical Faculty, Çanakkale Onsekiz Mart University, Çanakkale, Turkey.

Introduction
Isolated ACTH deficiency (IAD) is a rare disease which is characterized by secondary adrenal insufficiency with low cortisol production and normal secretion of pituitary hormones except ACTH. Isolated ACTH deficiency has rare association with Hashimoto’s disease which is characterized by autoimmune origin. This suggests the possibility of common autoimmune process affecting both the pituitary and the thyroid gland. We report a case of IAD with Hashimoto’s disease in a patient who presented with anorexia, nausea, vomiting and weight loss.

Case report
A 84 year-old man presented with anorexia, nausea, vomiting and weight loss for the last 3 months. His endoscopy revealed a Mallory-Weiss tear in esophagus. Sclerotherapy was performed. The laboratory test established hypothyroidism with plasma levels of free T3 of 1.89 pg/ml (1.71-3.71), free T4 of 0.47 ng/ml (0.7-1.48) and high TSH of 19.2 µIU/ml (0.35-1.94). The autoimmune antibodies were positive and the patient’s level of cortisol was found 1.22 µg/dl. ACTH levels were determined as 3.4 pg/ml. The patient was diagnosed with secondary adrenocortical insufficiency. We examined the other pituitary hormones such as FSH, LH, prolactin and GH which were in normal limits. DHEA-S level was found 4.3 mmol/l (E: 80–560). The magnetic resonance of pituitary imaging was normal. Hydrocortisone and l-thyroxine supplementation improved his symptoms.

Conclusion
Isolated ACTH deficiency is a rare cause of adrenal insufficiency which can be associated with Hashimoto’s thyroiditis that may present with severe gastrointestinal symptoms such excessive vomiting.

DOI: 10.1530/endoabs.32.P263

P264
Cases with adrenocortical carcinoma
Gülcin Cengiz Eceenis, Elif Kılıç Kar, Çigdem Tura Bahadır, Aysegül Atmaca, Hüsnü Atmaca & Raif Atmaca
Endocrinology Department, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey.

Introduction
Adrenocortical carcinoma (ACC) is a rare cancer (estimated incidence, 0.7 to 2.0 cases per 1 million population per year) with a poor prognosis. Even after seemingly complete surgical resection, most patients develop recurrence within 5 years. The 5-year survival rate is <15% among patients with metastatic disease.

Methods
We present the results of six patients with adrenocortical carcinoma followed in our clinic.

Results
The mean age was 54 years and female/male ratio was 2/4. Tumor size ranges from 6 to 14 cm. At baseline, only one patient had high dehydroxyepiandrosterone-sulphate levels (Patient 1). Tumor was non-functional in 5 patients. One patient presented with Cushing’s syndrome and hypercortisolism was documented in her laboratory evaluations (Patient 4). All of them were treated with surgery. In one patient, tumor was bilateral and in others were on left adrenal. The patient with bilateral tumors had lung metastasis at diagnosis (Patient 3). Another patient developed lung metastasis 2 years after the operation (Patient 1). Patient 4 had lung metastasis and Patient 6 had lung, liver and lymph node metastasis. One patient was lost-to follow-up after the operation (Patient 5). Three patients died 5 months after the operation. Three out of six patients received mitotane after the operation. Two patients could not receive mitotane because of elevated liver enzymes (Patients 4 and 6). Patient 1 developed lung metastasis 2 years after the diagnosis and is now receiving chemotherapy (cisplatin-etoposide) with mitotane. This patient is being followed in our clinic for 53 months.

Conclusion
Treatment options for advanced ACC are limited. Even after successful complete excision of the tumor, local or distant metastatic recurrences are frequent. However, some patients on regular follow-up and mitotane as adjuvant therapy may benefit from treatment as seen in Patient 1.

DOI: 10.1530/endoabs.32.P264

P265
Differential diagnosis of an incidental pituitary lesion detected with PET-CT in a patient with a known history of metastatic maxillary sinus tumor
Husniye Basır, Neslihan Cuhaç, Elif Ozdemir, Fatma Sağlam, Reyhan Ersoy & Bekir Cakı
1Department of Endocrinology and Metabolism, Atatürk Education and Research Hospital, Ankara, Turkey; 2Department of Nuclear Medicine, Atatürk Education and Research Hospital, Ankara, Turkey.

Introduction
Metastatic pituitary tumors are seen rarely and it is hard to differentiate them from the benign lesions of the gland. We have reported a case, with a known maxillary sinus tumor, detected to have a pituitary lesion coincidently on PET-CT.

Case
45 years old male patient with a known history of relapsed maxillary sinus tumor has been referred to our clinics because of the pituitary lesion detected to have increased FDG involvement on PET-CT examination. He was operated for the maxillary sinus tumor 35 years ago and had the second operation last year because of the recurrence. Histopathological examination was reported as well-differentiated squamous cell carcinoma with perineural and lymphovascular invasion. There was a tissue defect on the right maxillary region, nose and the right eyelid in physical examination. Pituitary lesion was metabolically active on PET-CT and SUV max value was 11.7. We have demanded a pituitary MRI and detected a 5.4×4.3 mm sized nodular pituitary lesion on the right side of the gland, which was isointense on T1A and T2A images and with late contrast concentration on dynamic sequences. In laboratory examination, anterior pituitary functions are in normal ranges. There wasn’t any symptom or sign of diabetes insipidus. Tissue biopsy for the definitive diagnosis could not be performed because of the facial defect.

Conclusion
It is difficult to differentiate metastatic lesions from the benign lesions of the pituitary gland. Most of the metastatic lesions are asymptomatic although presences of diabetes insipidus or ophthalmoplegia are suspicious for metastasis. Also, there isn’t any specific radiologic sign for metastatic lesions. In our case because of the lesion being metabolically active on PET-CT with a high SUV max value, isointense appearance on MRI and a history of maxillary sinus malignancy made us suspect pituitary metastasis.

DOI: 10.1530/endoabs.32.P265

P266
Secondary hypertension and hirsutism as a clinical manifestation of the tumor duplicit: case report
Zdenek Fryšák, David Karasek, Igor Hartmann & Ladislava Kacerova
1Department of Internal Medicine III – Nephrology, Rheumatology and Endocrinology, Faculty of Medicine and Dentistry, University Hospital of Olomouc, Olomouc, Czech Republic; 2Department of Urology, Faculty of Medicine and Dentistry, University Hospital of Olomouc, Olomouc, Czech Republic; 3Department of Clinical and Molecular Pathology, Faculty of Medicine and Dentistry, University Hospital of Olomouc, Olomouc, Czech Republic.

Endocrine Abstracts (2013) Vol 32
Differential diagnostic search for the pathogenetic causes of hirsutism and the combination of hypertension can provide very interesting results for the clinicians. The case report demonstrates a patient suffering from two hormonally active tumors – adrenal adenoma with primary aldosteronism and primary Leydig cell ovarian tumor with hyperandrogenism. The task of the authors was easier due to the perimenopausal age of the proband. Selective venous sampling was very helpful in diagnosis of these endocrine active tumors. Both of them were resolved by a single laparoscopic surgery. The combination of the two described tumors is really unique clinical finding. The solution using laparoscopy in a single procedure provided an elegant and efficient therapeutic approach.

DOI: 10.1530/endoabs.32.P266

**P267**

**Treatment dilemmas of Cushing disease: case report**

Joana Saraiva, Isabel Paiva, Maria Alves, Sofia Gouveia, Carolina Moreno, Daniela Guelho, Leonor Gomes, Manuela Carvalheiro & Francisco Carrilho

**Centro Hospitalar E Universitário De Coimbra, Coimbra, Portugal.**

**Introduction**

Cushing’s disease (CD) is a Grave disease that requires a multidisciplinary and individualized treatment approach.

**Case report**

We describe the case of a 31-years old female patient with Cushing disease diagnosed in 2007. She initially complained of weight fluctuations, amenorrhea, rounded face with plethora and acne, for 1 year duration. Analytically: 0800 h plasma cortisol of 14 m g/dl and 15 pg/dl; UFC 86 μg/24 h; 2 days LD-DST cortisol <0.1 μg/dl. No residue in MRI. Follow-up until 11/2009 revealed fluctuating clinical symptoms with periods of depression, acne and weight gain. She also had osteoporosis and renal calculi. UFC: 45, 135, 85, 166 and 210 μg/24 h. Plasma cortisol after 2 day LD-DST: 6.6 μg/dl. MRI: possible small lesion, not confirmed in MRI of 3/2010. Nevertheless, in 4/2010 she was submitted to a second TSS, without any corticotrophoma found. Hormonal evaluation (5/2010): plasma cortisol after 2 days LD-DST of 4.0 μg/dl, UFC 146–275 μg/24 h, no pituitary insufficiencies. Inferior petrosal sinus sampling wasn’t conclusive. MRI (11/2011) wasn’t suggestive of microadenoma. Since then and until 8/2012, worsening of clinical manifestations: menstrual irregularities, acne, depression, supraclavicular fullness, body bruising and osteoporosis. UFC 330 μg/24 h, 0800 h plasma cortisol 15 μg/dl and ACTH 26 pg/dl. Abdominal CT (7/2012): adrenal glands without alterations. As she maintains active disease bilateral adrenalectomy was proposed, to preserve fertility.

**Conclusions**

CD remains a challenge at diagnosis and causal treatment. Simultaneously is associated with severe morbidity (and mortality) related with the severity but also with the duration of the hypercortisolism. For young patients preservation of gonadal function is an important issue, leading to the sooner option for bilateral adrenalectomy.

DOI: 10.1530/endoabs.32.P267

**P268**

**Adrenocortical carcinoma: a case report**

Snezana Popovic-Pejcic & Anja Pejcic

1Clinic of Endocrinology, Diabetes and Metabolis Diseases, Banjaluka, Bosnia and Herzegovina; 2Clinic of Dentistry, Bernhard Gottlieb University, Vienna, Austria.

Adrenocortical carcinoma (ACC) is a rare (incidence 1–2 per 1 million population) and heterogeneous malignancy with incompletely understood pathogenesis, unknown etiology and poor prognosis. ACC tends to grow and metastasize rapidly if untreated. The majority of cases are incidental diagnoses of advanced stage disease that metastasizes precociously due to its tendency to invade vascular structures. Among adults presenting with hormonal syndromes due to tumor excess secretion, Cushing’s syndrome alone is most common, followed by mixed Cushing’s and virilization (glucocorticoid and androgen overproduction). Conn syndrome (mineralocorticoid excess) occur in <10% of cases. Our patients shows all symptoms of Cushing and Conn syndrome.

**Case report**

Patient is a 37-year-old woman with oncologic genetic lead. Patient presented with spontaneous fracture of the right femur and transferred to our clinic because of suspicion of ACC. Patient has one year progression of high blood pressure controlled with angiotensin-converting enzyme inhibitor. She complained also of diffuse postprandial abdominal pain with peaks of intensity accompanied with vomiting, aside from high blood pressure manifestations of muscle cramps, muscle weakness and headaches. Our patients is also presented with signs and symptoms of hormonal syndromes (Cushing syndrome, virilism and Conn syndrome).

Laboratory work-up including full blood count, blood chemistry, serum electrolytes, liver function tests, cortisol, aldosterone, normetanephrines, total metanephrines, and urine metanephrines. Ultrasound imaging revealed 90 × 83 × 88 mm left heterogenous adrenal mass that was confirmed with computer tomography and magnetic resonance. Histopathological result of adrenal mass reported adrenal carcinoma. Local invasion and tumor extension into the inferior vena cava as well as lymph node and left kidney or other metastases (lung and liver, peritoneum, colon, femur, mandible) are found. Palliative cisplatin-based chemotherapy and radiotherapy are alternative to surgical debulking. Ketoconazole is used to control hypercortisolemic symptoms and the therapy with i.v. bishophonate (Pamidronat 60 mg) is also given to prevent further pathological fractures.

DOI: 10.1530/endoabs.32.P268

**P269**

**Fountain of steroid deep within: a case report of an ectopic ACTH-producing tumor**

Tom Edward Lo, Imelda Antonio & Cecilia Jimeno

Philippine General Hospital, University of the Philippines, Manila, The Philippines.

**Background**

Cushing’s syndrome is defined as a hormonal disorder resulting from elevated serum cortisol leading to specific physical and biochemical abnormalities that might be detrimental to life itself. Majority is caused by steroid intake while endogenous sources although representing only a minority of patients often lead to delay in diagnosis. Ectopic ACTH syndrome considered a rare entity are usually found as small cell lung cancer and carcinoid tumors. Rare types of ectopic tumours are thymomas, pancreatic tumors, and medullary thyroid carcinomas. Knowing their rare presentations and diagnostic clues might help physicians in the future to easily diagnose and manage endogenous Cushing’s syndrome since most are completely reversible.

**Case summary**

A previously healthy 39 year-old Filipino female presented with rapid development of features compatible with Cushing’s syndrome (truncal obesity, buffalo hump, acne formation, moon facies, plethora, muscle wasting, acanthosis nigricans) in a span of 2 months. She also presented with metabolic alkalosis and significant hypokalemia leading to muscle paralysis. Significant hyperpigmentation of peculiar body sites (knuckles and toes) were observed. With further work ups and repeated hospitalizations, patient exhibited insulin resistance (secondary diabetes), hypertension, dyslipidemia and thyroid function abnormalities. Patient eventually referred to our institution for acutely worsening behavioural changes. Biochemical tests revealed elevated serum cortisol (12×), unexplained high dexamethasone suppression test and an elevated serum ACTH leading to a suspicion of a possible Ectopic-ACTH syndrome. Abdominal CT showed multiple liver masses. Patient eventually succumbed to nosocomial infection. On autopsy, an ectopic well differentiated neuroendocrine tumor was found at the pancreatic head with metastasis to the right hepatic lobe.

**Conclusions**

Knowledge of this disease and certain clinical clues and features (rapid clinical course, metabolic alkalosis with hypokalemia, severe hyperpigmentation, behavioural change) can guide clinicians to earlier diagnosis, rapid tumor location and immediate therapeutic initiation that can be life-saving.

DOI: 10.1530/endoabs.32.P269
Clinical case reports - Thyroid / Others

P270
Low TSH plasma levels and high fracture risk in postmenopausal osteoporosis and osteopenia patients
Renato Pastore & Daniela Mentuccia
UOC Endocrinology, Ospedale Fatebenefratelli, Isola Tiberina, Rome, Italy.

Introduction
Bone loss in thyroid dysfunction was first described by von Recklinghausen. Elevated bone turnover and decreased bone mass result when thyroid hormone levels are high and TSH levels suppressed. The changes in bone mass are impressive even in patients with subclinical hypothyroidism, where thyroid hormones are within the normal range, but TSH is low or undetectable. Evidence show that endogenous and exogenous TSH suppression is associated with an increased fracture risk.

Methods
We studied 1487 postmenopausal women (average age 65.47±9.94). TSH (0.3 to 4.2 μIU/ml) were correlated with the prevalence of vertebral fractures, classified by morphometric study. Postmenopausal patients showed different thyroid functional status. They received DXA examination and fulfilled WHO criteria for Osteoporosis.

Results
Osteoporosis was diagnosed in 587 patients (39.5%), osteopenosis in 875 (58.8%). In osteopoenic group 148 women (10%) showed vertebral fractures, while 645 osteoporotic patients (42.7%) had fractures. In addition, ‘major’ vertebral fractures (>25%) were present in 170 patients (11.4%) with subclinical hypothyroidism (TSH <0.3 μIU/ml). This result was compared to group of 60 women (4%) that showed TSH >0.3 μIU/ml (total percentage significant (P<0.05)). There was a correlation between subclinical hypothyroidism and BMD t-score values (correlation, Spearman’s ρ=0.18 is P<0.001).

Conclusions
Our data suggest the relationship between TSH plasma levels and vertebral fractures in women with postmenopausal osteoporosis and osteopenia. Because of the strong correlation between low TSH levels and high fracture risk, which appears to be dissociable for long-term decrements in BMD, we suggest maintaining TSH levels during replacement therapy to above 1 mU/ml, unless there is a clinical rationale for TSH suppression as in thyroid cancer patients. In these patients, admittedly without clinical evidence of efficacy, we propose the empiric use of an oral biphosphonate to prevent the high turnover osteoporosis and associated fracture risk.

DOI: 10.1530/endoabs.32.P270

P271
Malignancy rate of thyroid nodules, which defined as follicular lesion of undetermined significance and atypia of undetermined significance in thyroid cytopathology and relation with ultrasonographic features
Fatma Neslihan Cuhaci1, Dilek Arpaci1, Rifki Ucler1, Gulten Kiyak2, Samet Yalcin3, Pamir Eren Ersoy4, Gulnur Güler5, Reyhan Ersöz5 & Bekir Cakir6
1Department of Endocrinology and Metabolism, Ataturk Education and Research Hospital, Ankara, Turkey; 2Department of General Surgery, Ataturk Education and Research Hospital, Ankara, Turkey; 3Department of General Surgery, Yildirim Beyazit University, Ankara, Turkey; 4Department of Pathology, Yildirim Beyazit University, Ankara, Turkey; 5Department of Endocrinology and Metabolism, Yildirim Beyazit University, Ankara, Turkey.

Introduction
Fine needle aspiration cytology (FNAC) has been widely accepted the most accurate, safe and cost-effective method for evaluation of the thyroid nodules. The most challenging category in the FNAC is atypia of undetermined significance (AUS) and follicular lesion of undetermined significance (FLUS). Bethesda System (BS) recommends repeat FNAC in that category due to their low risk of malignancy. In our study, we aimed to investigate the malignancy rate of thyroid nodules of AUS and FLUS and to evaluate the presence of biochemical, clinical and echographic features possibly predictive of malignancy related to AUS and FLUS.

Materials and methods
Data of 268 patients operated for AUS and FLUS cytology were screened retrospectively. Ultrasonographic features and thyroid function tests, thyroid antibodies, scintigraphy and histopathological results were evaluated.

Results
Two hundred and seventy six nodules of 268 patient’s results are evaluated. Malignancy rates were 24.3% in the AUS group, 19.8% in the FLUS group and 22.8% in both group. In the evaluation of all nodules the predictive features of malignancy are hypoechoegenicity and peripheral vascularization of the nodule. In the AUS group, the predictive feature of malignancy is only hypoechoegenicity, and peripheral vascularization in the FLUS group.

Conclusion
We determined that the malignancy rates in these nodules are higher than the anticipated literature rate. This high ratio may be due to the fact that we studied only patients who underwent surgery. The ultrasonographic features alone may be insufficient to predict the malignancy, therefore all the clinical and ultrasonographic features must be considered in the evaluation of the thyroid nodules. In addition, we think that, the recommended management of repeat FNAC in these groups must be reconsidered with the clinical and ultrasonographic features.

DOI: 10.1530/endoabs.32.P271

P272
Recurrent pregnancy induced hypercalcaemia resulting in multiple terminations of pregnancy
Ganesh Chockalingam
The Canberra Hospital, Canberra, Australian Capital Territory, Australia.

Introduction
Pregnancy is characterized by increased intestinal calcium absorption, normal ionized or albumin-corrected calcium, high calcitriol, low PTH, gradually increasing PTHrP and hypercalcaemia. These differing hormonal changes can lead to nonclassic presentations of disorders of bone and mineral metabolism.

Case report
First-trimester 34-year-old multigrida patient presented with hyperemesis, abdomeinal pain, polyuria, polydipsia, leg cramps and constipation. Hypercalcaemia (4.13 mmol/l) with suppressed PTH was found while she was not taking any calcium. 25OH-VitD was low (40 nmol/l) and ACE level normal. 24 h urinary calcium and serum1, 25OH-VitD1 were elevated. PTHrP was not consistently elevated which may be related to the reliability of the assay itself. Imaging of breast, trunk revealed no evidence of maternal malignancy. BMD scan Hip T score was –1.7 and Z score –1.5 but Lumbar spine was normal. I.v. fluid therapy led to brief symptomatic improvement. Course of prednisolone failed to suppress calcium. Safety of bisphosphonates in pregnancy not established. Decision was made for medical termination of pregnancy (TOP) at 17 weeks from lack of symptomatic control of hypercalcaemia and the concern of its effect on the foetus. Calcium, PTHrP and 1,25OH-VitD levels normalised post termination. Foetal autopsy revealed no abnormalities apart from placental membrane calcification.

Discussion
There was no documented hypercalcaemia in previous pregnancies with former partner. She conceived twice again with a resultant miscarriage at 8 weeks and TOP at 7 weeks. The usual causes of hypercalcaemia were excluded. This appears to be a pregnancy-related phenomenon, and postulated mechanisms are either excessive calcium gut absorption due to increased sensitivity to 1,25 Vitamin D or an occult source. Could this be related to aberrant prolacin receptors with resultant high PTH and altered gene transcription. There were limited studies in 2009 assessing the role of bisphosphonates or other drugs in pregnancy.

DOI: 10.1530/endoabs.32.P272

P273
Familial Graves’ disease; case report
Ana Mota1, João Martins2, Sónica Vale1,2, Ana Martins3, Ana Gomes4, Gabriel Miltenberger-Milleini5,6,7 & Isabel Carro1,2
1Santa Maria’s Hospital, Lisbon, Portugal; 2Lisbon Medical School, Lisbon, Portugal.

Introduction
Graves’ disease is an autoimmune condition with an estimated prevalence of about 2%, 5–10 times more frequent in females. A multifactorial nature is

Endocrine Abstracts (2013) Vol 32
A 36-years-old male with mild hypertension was diagnosed with pseudocystic tumor (67 mm) in pancreatic region and liver metastasis in April 2010. One month later, the extirpation of retroperitoneal mass and metastasis was performed in local medical centre. Pathohistological diagnosis was metastatic paraganglioma. In June 2010, he was transferred to our Institution, and (111) -metaiodobenzylguanidine (MIBG) scintigraphy was negative. However ((18) F) fluorodeoxyglucose positron emission tomographic (18-FDG-PET) CT scanning showed on area (SVII) of uptake within the liver. In March 2011, multiple focal liver lesions were detected by MSCT scan, which were negative on In-111 octreoscan and MIBG scintigraphy. Urinary adrenalin, noradrenalin and dopamine were normal, while chromogranin A level was elevated. Germline nonsense mutation was identified in exon 2 (R27X) of succinate dehydrogenase B (SDHB) gene. Patient’s father and younger brother were carriers of the same mutation.

At the same time period, we tested patient’s, 2-years younger brother who carried the same germ-line mutation. He suffered from hypertension since he was fourteen. Retroperitoneal mass (9.5 cm) was detected at the age of seventeen by echography. In January 2008, extraction of retroperitoneal tumor was performed in local medical centre, and during the surgical procedure the rise in blood pressure was recorded. Histopathological diagnosis was metastatic paraganglioma. He came to our clinic in May 2010 without any symptoms. Abdominal MSCT revealed liver metastases. Although MIBG scintigraphy and In-111 octreoscan did not show uptake, an (18) F-FDG-PET/CT showed multiple areas of uptake in liver. Urinary adrenalin, noradrenalin and CgA were normal and urinary dopamine was slightly elevated. Both brothers continued treatment with sunitinib and partial remission was registered after 3 months. This nonsense germline mutation in SDHB gene (R27X) is associated with the similar phenotype and the similar response after sunitinib administration in both patients.

DOI: 10.1530/endoabs.32.P274

P275

Submandibular ectopic thyroid gland

Marta Domínguez-López, Inmaculada González-Molero, MSol Ruiz & Federico Soriguer

Carlos Haya Hospital, Málaga, Spain.

Introduction

Ectopic thyroid glands are generally a rare entity appearing mostly in the cervical midline (90% of the cases) and even more rarely in other anatomical sites (10%).

Clinical report

We present the case of an ectopic submandibular thyroid gland. A 31-year-old woman was referred to our department with a history of left submandibular swelling.

A scintigraphy was performed, which showed an accumulation of activity in the right submandibular region without any evidence of further thyroid tissue in the normal site.

Preoperative FNA revealed benign ectopic thyroid tissue. Hormonal laboratory test showed normal thyroid function. The patient was submitted to resection of the mass. Histological examination of the specimen confirmed the diagnosis.

A substitution treatment with thyroxin was initiated postoperatively, as this was the only functional thyroid tissue.

Conclusion

Physicians should be aware of the possibility that a submandibular swelling could be an ectopic thyroid gland. This entity poses specific diagnostic and therapeutic difficulties. Thorough preoperative diagnostics and resection of the ectopic tissue guarantee a good outcome. Physicians should also consider that this ectopic gland is the only functional thyroid tissue in 70% of cases.

DOI: 10.1530/endoabs.32.P275

P276

Barraquer-Simons syndrome

Maria Fatima Baracho1, Maria Goreti Santos1, Beatriz Amaral1, Raissa Carmo1, Renata Rafael1, Luciana Melo1, Maria Augusta Araujo1, Gemma Santos1, Antonio Oliveira-Filho1 & Adriana Nunes1

1University of Rio Grande do Norte, Natal/RN, Brazil; 2Municipal Consortium, Picui/PB, Brazil.

The Barraquer-Simons syndrome is a rare form of partial symmetric lipodystrophy with involvement of the face and upper body, of unknown cause, characterized by loss of subcutaneous fat in the face and started stretching for the upper body.

Case report

Female patient, 26 years old, presenting morphologic change in facies, chest, upper limbs, lower limbs and abdomen since she was 10 years old. Last year, she has increased weight at 30%, with apparent muscle hypertrophy, facial hypertrichosis and decreased libido. Physical examination shows normal thyroid palpation, absence of umbilical hernia and bone abnormalities. Menarche at 13 years, with regular menstrual cycles. Deafness and epilepsy were excluded. Comment

The Barraquer-Simons syndrome was described in 1904, predominantly affects females (4:1), and the appearance of symptoms commonly happens at the end of the first or beginning of the second decade of life. Its origin is unclear, but associations have been made with genetic mutations, neuroendocrine disorders and autoimmune diseases. Most cases appear to be isolated in their families. Occasionally, functional abnormalities such as deafness, epilepsy, mental retardation, neuropathy, myopathy, and vascular disease may be associated with dermatomyositis. Diagnosis is mainly clinical and their distinctions with other syndromes such as Cockayne, SHORT, Berardinelli-Seip syndrome and bilateral Parry-Romberg. Currently, facial reconstruction techniques have been used to restore facial contours, and the disease management must include the monitoring and treatment of complications, because it is a phenocopy of other syndromes such as lipodystrophy which presents diabetes and hypertriglyceridemia. Barraquer-Simons syndrome is quite rare disease, mainly producing facial changes, to which are directed most of the treatments, however studies should be conducted to clarify the pathophysiology of the disease.

DOI: 10.1530/endoabs.32.P276
**P277**

**Dural ectasia accompanying a case of multiple endocrine neoplasia type 2B**

İhan Anaforoğlu, Ekrem Altun & Mustafa Köse
Department of Endocrinology and Metabolism, Trabzon Kanuni Education and Research Hospital, Trabzon, Turkey.

**Introduction**

Manifestations of MEN2B include medullary carcinoma of thyroid (MCT), pheochromocytoma, and a number of somatic mutations like marfanoid habitus, mucocutaneous neuromelanocytosis of the bowel. Dural ectasia results from enlargement of the spinal canal, which was identified in 63–92% of patients with Marfan syndrome, however, it was not previously described in MEN2B. We detected dural ectasia in our patient with MEN2B.

**Case report**

A 28-year-old woman was admitted with abdominal discomfort. Bilateral adrenalectomy was performed because of pheochromocytoma. Dural ectasia was detected incidentally at sacro-iliac region. Calcium ion level was detected to be normal, her neck ultrasonography was negative for recurrence of MCT. After bilateral adrenalectomy, she was started on hydrocortison and her urinary catecholamine metabolites were detected as normal.

**Conclusion**

Patients with MEN2B have development abnormalities, a decreased upper/lower body ratio, skeletal deformations, joint laxity, Marfanoid habitus, and mycelylated cornal nerves. Disturbances of colonic function are common, including chronic constipation and megacolon. Dural ectasia can be seen in anchylosing spondylitis, achondroplasia, Larsen-Denys syndrome and in the vascular form of Ehlers-Danlos syndrome besides Marfan syndrome. This abnormality results from enlargement of the spinal canal owing to progressive ectasia of dura and neural foramina and to erosion of vertebral bone, it involves lumbarosacral spine. To our knowledge, this is the first case of coexistence of MEN2B and dural ectasia.

**DOE:** 10.1530/endobas.32.P277

---

**P278**

**Coexistence of euthyroid ophthalmopathy and isolated ocular myasthenia gravis in a patient with vitiligo: a challenging diagnosis of APS-3C**

Ileana Duncea, Ioana R Ilie, Monica Goia-Socol, Dana Gherghel & Carmen E Georgescu
Endocrinology Clinic, 6th Medical Sciences Department, 'Iuliu Hatieganu' University of Medicine and Pharmacy Cluj-Napoca, Cluj Napoca, Romania.

About 1% of the patients with Graves’ disease develop myasthenia gravis, however, euthyroid Graves’ ophthalmopathy has only rarely been associated with myasthenia gravis and especially with isolated ocular myasthenia gravis. A 63-year-old male patient with vitiligo presented double vision and right ptosis, shortly followed by left ptosis. On the ophthalmological examination there was bilateral ptosis and orbocto-ocular ultrasonography yielded a thickening of the left lateral recti. Electromiographic and extensive biochemistry examinations were normal. Thyroid dysfunction was absent with normal TSH receptor antibodies but antithyroid peroxidase antibodies titers were 82.88 IU/ml (normal < 34). Thyroid ultrasound examination showed a nodular goiter presenting diffuse decreased echogenicity. The ophthalmic examinations were interpreted as euthyroid-associated orbitopathy in the context of Hashimoto thyroiditis and the patient received a course of corticotherapy. Two months later he was admitted with bilateral exophthalmos and sclera and conjunctival injection and received combined glucocorticoid and radiotherapy. Two weeks after the corticotherapy was stopped, the patient experienced exacerbation of diplopia and bilateral palpebral ptosis. At a new neurologic assessment, repetitive nerve stimulation of the ulnar nerve recording from abductor digiti minimi of the right hand revealed a decremental response and serum acetylcholine receptor antibody was positive at 5 nmol/l (normal < 0.4). Chest X-ray and chest computed tomography did not reveal any thymic hyperplasia or thymoma. TSH was slightly reduced at 0.158 mU/l and anti-thyroglobulin antibody levels were 845 IU/l (normal ≤ 115). Pyridostigmine and intermittent glucocorticoid treatment was recommended. At 2-years follow-up visit, no signs of generalized myasthenia were detected. We report a case of euthyroid Graves ophthalmopathy associated with isolated ocular myasthenia gravis appearing in a patient with longstanding vitiligo, compatible with an autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. The coexistence of these two entities, in the absence of overt thyroid dysfunction or generalized features of myasthenia gravis may cause diagnostic confusion.

**DOE:** 10.1530/endobas.32.P278

---

**P279**

**Giant cell granuloma as initial presentation of primary hyperparathyroidism: a case report**

Sefika Burcak Polat1, Islaya Taskaldiran2, Berna Evranos1, Aydan Kulcsasian1, Elif Kaya1, Reyhan Ersoy1 & Bekir Cakir1
1Endocrinology Department, Atatürk Research Hospital, Beyazit University, Ankara, Turkey; 2Internal Medicine Department, Atatürk Research Hospital, Yildirim Beyazit University, Ankara, Turkey; 3Pathology Department, Atatürk Research Hospital, Yildirim Beyazit University, Ankara, Turkey; 4Faculty Of Dentistry, Gazi University, Ankara, Turkey.

Giant cell granuloma is a skeletal manifestation seen now rarely in hyperparathyroidism due to early recognition of the disease. Lesions usually occur in the areas of intense bone resorption. They can affect mandible, maxilla, clavicle, ribs and pelvic bones. Most of the patients who have primary hyperparathyroidism are asymptomatic and are discovered incidentally during laboratory examinations. Here, we represent a female patient who was referred to endocrinology clinics because of maxillary brown tumor detected by her dentist.

**Case**

Thirty-years-old female patient has admitted to dental clinics with the complaint of oral mass and accompanying symptoms as decreased appetite, weight loss and numbness on the jaw. Biopsy of the oral lesion was consistent with giant cell granuloma. Radiographic imaging has revealed multiple bone cysts on the mandible and maxillary bones. In laboratory exam, severe hypercalcemia and hypophosphatemia were detected. Her serum parathormon level and urinary calcium level were elevated. In ultrasonographic examination, we have detected two parathyroid adenomas on left side and MIIB scan was positive. In bone mineral densitometry, osteoporosis was detected at the lumbar vertebrates. She didn't have any renal stones in abdominal ultrasonography. We have searched for MEN1 syndrome. There was a microadenoma in pituitary MRI that was proven nonfunctional with hormone tests. Her upper gastro intestinal endoscopy was normal as the serum gastrin levels. She underwent surgery and all parathyroid glands and thymus were excised then 1/2 of a parathyroid gland was seeded on forearm. No complications occurred during or after surgery and she was discharged and referred to her dentist for curettage of the bone cysts.

**Treatment of parathyroidism is surgery. However, treatment for bone lesions is controversial. They can regress after removal of the adenoma. In the persistent cases, surgical removal of the bone lesion after a short course of steroid therapy is advised.**

**DOE:** 10.1530/endobas.32.P279

---

**P280**

**Fibrous variant of Hashimoto’s thyroiditis: development of neck fibrosis and mediastinal fibrosis**

Albert Makarov1,2, Violeta Arzhakova1,2, Peter Neustrove1 & Elena Makarova2
1North-Eastern Federal University named after M K Ammosov, Yakutsk, Russia; 2National Center for Medicine, Yakutsk, Russia.

Immunoglobulin G4-related disease (IgG4-RD) is now a widely recognised multi-organ system disease characterised by elevated serum and tissue concentrations of IgG4. Two forms of thyroid involvement in IgG4-RD have been described, including Reidel’s thyroiditis (IgG4-related thyroid disease) and the fibrous variant of Hashimoto’s thyroiditis.

**Objective**

To describe a case of the development of massive neck fibrosis and mediastinal fibrosis in a patient with the fibrous variant Hashimoto’s thyroiditis.

**Methods and case presentation**

In January 2012, a 59-year-old woman with a 1-year history of subclinical hypothyroidism due to Hashimoto’s autoimmune thyroiditis was admitted to our department, presenting with a swelling in the anterior region of the neck, dyspnea, dysphagia, fatigue. The tumor progressed quickly to a ecklare, stony hard mass on the anterior neck region. Analysis: TSH: 0.42 mU/l, FT₃, 13.90 pmol/l;
AbTPO, 133.92 U/ml, erythrocyte sedimentation rate (ESR), 58 mm/h; Echo-guided FNAB confirmed the diagnosis of Hashimoto thyroiditis and neck fibrosis. A computed tomography (CT) revealed a fibrotic mass located at the anterior inferior aspect of the neck and mediastinum with displacement of the tracheal lumen and stenosis of esophagus. We started therapy with prednisolone 60 mg daily and l-thyroxine substitution therapy. The follow-up lasted for 12 months. After 1 month of corticosteroid therapy, the patient had no compression symptoms. The treatment with prednisolone led to a significant subjective improvement and objective changes (a significant decrease of neck and mediastinal fibrosis), confirmed by regular clinical examinations, ultrasonography and computed tomography of the neck and mediastinum. Now the patient is in good health, undergoing a therapy with prednisolone 5 mg daily.

Conclusion

We have reported an unusual case of development of the massive neck fibrosis and mediastinal fibrosis in a patient with Hashimoto’s thyroiditis, which showed good response to steroid treatment. It is important for the physician to recognize the presence of mediastinal fibrosis in the presence of fibrous variant of Hashimoto’s Thyroiditis and initiate steroid therapy for resolution of both diseases.

DOI: 10.1530/endoabs.32.P280

P281

Differentiated thyroid cancer presenting as chylothorax

Carolina García-Figuera1, Manuel Cayón2 & Pedro Gallego1

1Internal Medicine Unit, Hospital SAS, Jerez de la Frontera, Spain; 2Endocrinology and Nutrition Unit, Hospital SAS, Jerez de la Frontera, Spain.

Introduction

Initial presentation of thyroid carcinoma can range from a solitary thyroid nodule or cervical lymphadenopathy to symptoms related to local compression. Presentation as chylothorax due to compression of thoracic duct is exceptional. The aim of this case report is to describe an extremely rare case of follicular thyroid cancer presenting as chylothorax with special attention to therapeutic aspects.

Case report

A 78-years-old woman was referred to Internal Medicine Unit for evaluation of pleural effusion. She had a several months history of cough and dyspnea on exertion. Medical history was significant for hypertension and atrial fibrillation. Physical examination revealed a massive pleural effusion. pleural fluid with the typical milky appearance of chylothorax. The diagnosis of chylothorax was confirmed by measuring the triglyceride levels of pleural fluid (469 mg/dl). A chest tube was placed in the right pleural space and parenteral nutrition was started. Fine-needle aspiration of thyroid mass was negative for malignancy. A transcervical approach to removal her substernal goiter was performed.

A sternotomy was not required for removal and no thoracic duct repair or ligation was necessary. Biopsy of the thyroid mass was positive for follicular carcinoma without evidence of metastases. Chest tube was removed and oral nutrition was reintroduced. The patient received radioiodine ablation and postoperative follow-up showed no residual chylothorax.

Conclusions

It is rarely described the association of chylos pleural effusion and thyroid cancer. To the best of our knowledge this is the first case of follicular carcinoma presenting as chylothorax. The current case also highlights the potential surgical treatment of chylothorax associated to substernal goiter through transcervical approach without need of thoracic duct repair.

DOI: 10.1530/endoabs.32.P281

P282

A case of confirmed Smith–Lemli–Opitz syndrome

Imre Zoltán Kuti1, Zsuzsanna Szántó1, Ildikó Lüdke1, Gabriela Duka1 & Vasilica Plaiasu1

1Clinical Section of Endocrinology, University of Medicine and Pharmacy, Targu Mures, Romania; 2Private Pediatric Ambulatory Unit, Targu Mures, Romania; 3Institute for Mother and Child’s Protection, Bucharest, Romania.

Smith–Lemli–Opitz syndrome (SLOS) is a 46,XY disorder of sex development, included in the subgroup of disorders in androgenesis syndrome. The disease is caused by mutations of 7-dehydrocholesterol reductase (DHCR7) gene, conducting to deficient synthesis of the correspondent enzyme and of cholesterol, with important role in embryogenesis, adrenal and gonadal steroidogenesis. Clinical manifestations include facial dysmorphism, syndactyly, ambiguous external genitalia and visceral malformations. We present the case of an infant born by cesarean section for fetal suffering (Apgar score 8/1–8/5), with multiple malformations (dysmorphic face, polydactyly, syndactyly, hypospadias, cryptorchidism) detected already at birth. Investigations diagnosed small atrial septal defect and corpus callosum agenesis was suspected. The clinical examination at 4 months of age showed growth failure, dysmorphic face, bilateral ptosis and epicanthus, generalized muscle hypotony, asymmetrical polydactyly (complete on right hand, partial on left hand), bilateral “Y” shaped syndactyly of the second and third toes, micropenis, hypospadias, small scrotum, cryptorchidism, neuro-reflexo-motorical developmental level of 1 month, psychical and verbal developmental level 2–3 months. Normal cortisol at baseline (17.18 μg/dl; n: 6.4–21), low total testosterone (0.74 mg/ml) and DHEA-S (3.1 μg/dl; n: 3.4–123.6), high LH (5.22 mU/ml; n: 0.5–4) were measured. Cholesterol was reduced (total cholesterol 79 mg/dl, HDL-cholesterol: 9.2 mg/dl), and in context of dysmorphic facies and anomaly of external genitalia the suspicion of SLOS rises. The karyotype is 46,XY 47/48. Mutation analysis of DHCR7 gene (chromosome 1q13.2–q13.5) identified two heterozygous mutations: c.452G>A (p.Trp151X) and c.278C>T (p.Thr93Met), this case being the first genetically confirmed SLOS in our country. An adequate diet, neurological recuperation, neurotrophic treatment, and endocrino-metabolic follow-up was recommended.

DOI: 10.1530/endoabs.32.P282

P283

A case of generalized resistance to thyroid hormone with chronic thyroiditis

Tatiana Shestakova, Alexander Dreval & Irina Komerud

Moscow Regional Research Clinical Institute n.a. Vladimirsyky, Moscow, Russia.

Introduction

Resistance to thyroid hormone (RTH) is a rare disorder characterized by reduced tissues’ responsiveness to thyroid hormones (TH). Usually patients with RTH have not clinical signs except goiter. We describe a 70-years old woman with RTH and autoimmune thyroiditis simultaneously.

Case report

Woman 70-years old was hospitalized in our department on August 2011 with suspicious of Thyrotropinemia because of high levels of TSH and FT4. The patient has atrial fibrillation controlled by the β-blockers since 2006. At that time only TSH was assessed – 6.8 mU/l (0.4–4.0) and FT4 118.4 pmol/l (11–23), T3 – 14.7 nmol/l (1.4–4.0), AbTPO – 515 U/l (0–30). Thyroid US revealed a goiter – 50 ml, inhomogeneous, without nodules. There were no any clinical symptoms of thyrotoxicosis except normosystolic atrial fibrillation (on β-blockers). We confirmed high levels of TSH and TH. Pituitary MRI with contrast was normal. We supposed that patients will be hypothyroid in the future.

Conclusion

In this case, we have two different conditions: RTH and autoimmune thyroiditis. We supposed that patients will be hypothyroid in the future.

DOI: 10.1530/endoabs.32.P283
P284

Autoimmune hypothyroidism converted to hyperthyroidism: is it a common phenomenon?
Saira Furqan & Najmul Islam
Aga Khan University Hospital, Karachi, Pakistan.

Introduction
Graves’ disease and Hashimoto’s thyroiditis are the two autoimmune spectrum of thyroid disease. Cases of conversion from hyperthyroidism to hypothyroidism have been reported but conversion from hypothyroidism to hyperthyroidism is very rare although reported. We report a case of hypothyroidism that converted to a hyperthyroid state needing treatment.

Case report
A 36 years old female presented with a 3 months history of easy fatigability, cold intolerance, polynororrhagia, constipation and weight gain. On examination she had bradycardia and dry skin. Thyroid gland showed small diffuse enlargement. Clinical suspicion of primary hypothyroidism was made and then confirmed by TSH of > 50 uIU/ml (0.4–4.2 uIU/ml) with FT4 value of <0.30 ng/dl and positive thyroid antibody titre. Thyroxine was started at 100 µg/day. Gradually requirement of thyroxine decreased and she maintained her TSH within normal range on 50 µg/day of thyroxine. After 3 years dose was further reduced to 25 µg/day but after 2 years again thyroxine dose was increased to 50 µg/day because of slightly increased TSH of 8.86. Slightly more than a year later she presented with weight loss of 3 kg and feeling of anxiety and tremors of hands. TSH was < 0.005 with a FT4 of 2.4 confirming the state of thyrotoxicosis. Thyroxine was stopped and patient was observed over a period of 6 months. She remained clinically and biochemically hyperthyroid with a repeat TSH of <0.005 and FT4 of 2.66. Thyroid scintigraphy showed an increased homogenous tracer uptake. She was started on Carbimazole and she remains on it till date.

Conclusion
This case demonstrate that high index of suspicion should be there if a patient with primary hypothyroidism develop persistent symptoms of hyperthyroidism. Otherwise it can be missed easily considering it as an over replacement with thyroid hormone.

DOI: 10.1530/endoabs.32.P284

P285

Maturity onset diabetes of youth (MODY) in a patient with VATER syndrome
Panagiotais Anganostis, Zoe Elisfathiou, Maria Poulosouchidou & Marina Kita
Department of Endocrinology, Hippokration Hospital of Thessaloniki, Thessaloniki, Greece.

Introduction
VATER syndrome is a rare, usually sporadic, entity, including ≥ 2 of the following: vertebral defects (V), anal atresia (A), tracheoesophageal fistula, esophageal atresia (TE) and radial or renal dysplasia (R). Maturity onset diabetes of youth (MODY) is a usually non-insulin-dependent type of monogenic diabetes mellitus (DM), usually in adults <25 years, with autosomal dominant inheritance, without the features of metabolic syndrome.

Case report
A 25-year-old Caucasian male with VATER syndrome was admitted to our department due to newly diagnosed DM on occasion of polydypsia and polyuria, without ketoacidosis (fasting plasma glucose (FPG) levels: 355 mg/dl, glycosylated hemoglobin (HbA1c): 12.6%). His family history was positive for non-insulin dependent DM (diagnosed at 35 years).

Clinical examination was remarkable for a low body mass index (18.28 kg/m²), muscular weakness of the extremities and hearing loss. Investigation for autoantibodies to glutamic acid decarboxylase (GAD), insulin, islet cells and tyrosine phosphatase (IA2) was negative.

During an oral-glucose-tolerance-test (OGTT), FPG, fasting insulin and C-peptide levels at baseline were: 150 mg/dl, 2 mIU/ml (normal: 6–27) and 1.07 ng/ml (normal: 0.9–7.1), and 2 h after glucose 75 g: 256 mg/dl, 11.7 mIU/ml and 3.38 ng/ml, respectively.

He was treated with glimepiride 2 mg/day. At 3 months, HbA1c fell to 5.9%. He remained on glimepiride for 1 year, when due to glucose control deterioration, insulin was started.

He fulfills the five criteria of MODY: early-age newly DM with normal insulin and C-peptide levels, positive family history for DM, >90 mg/dl increase in plasma glucose during OGTT, glycosuria with relatively normal FPG and responsiveness to sulfonylureas. Genetic analysis for MODY 3 (the most common) was negative. Further testing to rule out mitochondrial diabetes is under way.

Conclusions
This is the first case reporting the co-existence of MODY with VATER syndrome. The exact pathogenetic mechanisms linking these entities are currently unknown.

DOI: 10.1530/endoabs.32.P285

P286

Plasmapheresis in rapid preparation of a patient with toxic multinodular goiter for surgery
Feyza Yener Ozurturk, M Masum Canat, R Selvinaz Erol, Savas Karatas, Idris Kuzu & Yuksel Altuntas
Department of Endocrinology and Metabolism, Sisli Etfal Training and Research Hospital, Istanbul, Turkey.

Thyroidectomy is the definitive treatment for toxic multinodular goiter (TXMNG). Surgery should be performed when the patient is euthyroid which decreases perioperative cardiac risks. Plasmapheresis is a procedure that removes the thyroid hormones from the circulation. It is an alternative method in case of resistance or contraindications to anti thyroid drugs. Role of plasmapheresis in the treatment of TXMNG is not fully determined in the literature. We report a case with TXMNG who was prepared for surgery by plasmapheresis due to side effects of antithyroid drugs.

A 54-year-old female diagnosed as TXMNG was admitted to Sisli Etfal Training and Research Hospital. Endocrinology Clinics because of a complicated hyperthyroidism. While on propylthiouracil (PTU) therapy, she exhibited erythematous, tender nodules and plaques at bilateral lower extremities. PTU was stopped. Propylthiouracil related ANC:A(+) panniculitis was diagnosed based on biopsy and laboratory findings. On the 7th day of systemic steroid therapy, signs and symptoms of hyperthyroidism recurred (TSH:0.005 uIU/ml, FT3:7.77 ng/dl, FT4:9.49 pg/ml). Ultrasonographic examination revealed a diffusely enlarged thyroid gland with multiple nodules, right lobe extending retrosternally. Thyroid scintigraphy with 99 m technetium showed a hyperactive nodule in the left lobe and a hypotrophic nodule with a hyperactive component in the right lobe. Rest of the thyroid other than nodules showed high activity uptake. Methimazole 40 mg/day was started along with b-blocker. As euthyroidism could not be achieved on the 3rd week, plasmapheresis was decided for rapid preparation to surgery. The patient had seven sessions of plasmapheresis performed with filtration method (Infomed, CS-220, Switzerland). The replacement fluid was ten fresh frozen plasma for each session (totally 2000 cc). Although thyroid hormone levels could only moderately decreased, the patient was asymptomatic. The patient underwent surgery with b-blocker and dexamethasone treatment to avoid the thyroid storm in the perioperative period. Total thyroidectomy was performed successfully and adenomatous nodular hyperplasia was diagnosed pathologically.

Plasmapheresis can be considered a safe and effective alternative procedure to prepare patients with TXMNG for surgery when drug treatment fails or is contraindicated.

DOI: 10.1530/endoabs.32.P286

P287

Postmenopausal hirsutism and hyperandrogenemia due to granulosa cell tumor of the ovary
Cigdem Bahadir, Aysegul Atmaca, Hulusi Atmaca & Ramis Colak
Department of Endocrinology and Metabolism, Ondokuz Mayis University School of Medicine, Samsun, Turkey.

Introduction
Progressive baldness and severe hirsutism associated with granulosa cell tumor of ovaries are rare conditions in women. Reported cases are usually pubertal girls and young women. Here, we report a case of postmenopausal baldness and hirsutism due to granulosa cell tumor of the ovary.

Endocrine Abstracts (2013) Vol 32
Endocrine Abstracts (2013) Vol 32

P288
Clinical case report: male patient with SRY-positive 46,XX testicular disorder of sex development
Marta Domínguez-López, Immaculada González-Molero, Isabel Esteva, Montsearat Gonzalo-Marín, MSoledad Ruiz de Adana & Federico Soriguer
Carlos Haya Hospital, Málaga, Spain.

The 46 XX male syndrome (de la Chapelle syndrome or 46 XX testicular disorder of sex development -46,XX testicular DSD-) is a rare phenotype associated with disorder of the sex chromosomes. XX males exist in different clinical categories with ambiguous genitalia or partially to fully mature male genitalia, in combination with complete or incomplete masculinization.

Clinical report
We describe the clinical, molecular, and cytogenetic findings of a 26-year-old male patient with 46,XX testicular DSD.

The patient attended our endocrinology clinic with complaints of gynecomastia. His height was 165 cm and weight 76.6 kg (BMI: 28.13 kg/m²). He presented bilateral gynecomastia for the last 7 years. At presentation, hormonal laboratory evaluation revealed elevated serum concentrations of FSH and LH, with low concentrations of Testosterone (230 ng/dl). The testicles were descended in the scrotum but small in size with volumes 3.5 and 4 ml (normal range 18–30 ml). Semen analysis showed azoospermia. Chromosomal analysis revealed 46,XX karyotype. Fluorescence in situ hybridization (FISH) showed the SRY region translocated to the short arm of the X chromosome. The presence of the SRY gene was also confirmed by polymerase chain reaction (PCR).

Conclusion
The 46,XX testicular DSD is a rare form of sex reversal with complex mechanisms leading to a large spectrum of clinical manifestations ranging from ambiguous genitalia in the newborn to normal male phenotype. Therefore, diagnosis is established either pre- or early postnatal, or in adult life due to male infertility or as in our case, due to gynecomastia. Our patient has a 46,XX Karyotype, normal male phenotype and hypergonadotropic hypogonadism leading to infertility.

P289
Insulin autoimmune syndrome, IAS (Hirata disease) case report
Ganesh Chockalingam1, Dennis Wilson1 & Roderick Clifton-Bligh2
1The Canberra Hospital, Canberra, Australia; 2Royal North Shore Hospital, Sydney, Australia.

Introduction
Insulin autoimmune syndrome was first described in 1973 by Hirata, characterised by recurrent spontaneous postprandial hypoglycaemia. Serum insulin is extremely high with elevated insulin autoantibodies. More than 170 cases reported worldwide. We report the first case of IAS in Australia.

Case report
Eighty one-year old Argentinean woman with 3 month history of intermittent, late postprandial diaphoresis, tremors, palpitations, dizziness and confusion. Symptoms improved with sugary drinks and other caloric intake resulting in weight gain of 3 kg. At presentation blood glucose level (BGL) was 1.2 mmol/l and required 50% dextrose to maintain her BGL > 6. Serum insulin was > 2400 mU/l (normal < 27), C-peptide 11.7 mmol/l (0.4–1.5) and sulphonlurea screening was negative. Abdominal CT, MRI and Dotatate PET scan failed to identify an insulinoma. Endoscopic ultrasound found an 8 mm pancreatic lesion. Calcium stimulation study showed high insulin without a gradient. Laparotomy failed to show an insulinoma. Diagnosis of Hirata disease with elevated insulin autoantibodies > 50 U/l ( < 0.3) was treated with reducing prednisone dosage maintaining remission.

Discussion
Mechanism of IAS is that antibodies against insulin binds and releases insulin asynchronously. Free insulin levels are normal though bound (total) are high. Incidence of IAS in Caucasians is one-tenth of Japanese. Eighty percent of IAS patients spontaneously remit. In some individuals it is associated with exposure to sulphhydryl compounds interacting with disulphide bonds rendering insulin more immunogenic. IAS is strongly associated with HLA class II alleles. Insulinomas are the most prevalent cause of hyperinsulimemic hypoglycaemia in Caucasians. Investigation is focused on localization followed by surgery. Our case highlights important differential diagnosis, the need to measure insulin antibodies to avoid unnecessary surgery.

P290
Neurogenic hypertension as a case report
Tanja Nisic, Mira Stojkovic, Milos Stojoanic, Jasmina Ciric, Biljana Beleslin, Tiana Lalic, Milos Zarkovic & Bozo Trbojevic
Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of Serbia, Belgrade, Serbia.

Introduction
Neurogenic hypertension is associated with unilateral neurovascular compression of the brainstem and cranial nerves V, IX, X, VII, VIII. Causes may include nerve injury, vascular compression, tumors. Symptomatology seems hyperactive dysfunction syndrome of the cranial nerves. In the clinical picture, it can be seen trigeminal neuralgia, vertigo, tinnitus, hemifacial spasm, and in some cases hypertension.

Case report
Female patient, 45 years old, pianist, hospitalized in our department to investigate the etiology of hypertension. Symptoms began two years ago, while working at the computer, in the form of a sudden attack of vertigo, disorientation, anxious, with the simultaneous appearance of facial asymmetry (swollen left eyelid and down, left eyebrow and left corner of the mouth), and pain in the left side of the head, followed by high pressure 170/100 mmHg and tachycardia 120/min. The attack lasted about 20 min and passed spontaneously. Such attacks were two to three times a month and sometimes weekly. Between attacks she was healthy. The results of the functional and morphological studies show that the causes of the attacks are pathological changes in the pons. Examinations excluded renovascular and endocrine causes of hypertension. Magnetic resonance imaging of the head found a malformation of blood vessels in the border edge infratentorially midbrain and pons. Electroencephalogram was normal several times.

Conclusion
Neurogenic hypertension was the result of vascular compression of the cranial nerves and brainstem and treatment with Bisoprolol and Tegretol led to a reduction in the frequency of attacks.

DOI: 10.1530/endoabs.32.P289

P290
Neurogenic hypertension as a case report
Tanja Nisic, Mira Stojkovic, Milos Stojoanic, Jasmina Ciric, Biljana Beleslin, Tiana Lalic, Milos Zarkovic & Bozo Trbojevic
Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of Serbia, Belgrade, Serbia.

Introduction
Neurogenic hypertension is associated with unilateral neurovascular compression of the brainstem and cranial nerves V, IX, X, VII, VIII. Causes may include nerve injury, vascular compression, tumors. Symptomatology seems hyperactive dysfunction syndrome of the cranial nerves. In the clinical picture, it can be seen trigeminal neuralgia, vertigo, tinnitus, hemifacial spasm, and in some cases hypertension.

Case report
Female patient, 45 years old, pianist, hospitalized in our department to investigate the etiology of hypertension. Symptoms began two years ago, while working at the computer, in the form of a sudden attack of vertigo, disorientation, anxious, with the simultaneous appearance of facial asymmetry (swollen left eyelid and down, left eyebrow and left corner of the mouth), and pain in the left side of the head, followed by high pressure 170/100 mmHg and tachycardia 120/min. The attack lasted about 20 min and passed spontaneously. Such attacks were two to three times a month and sometimes weekly. Between attacks she was healthy. The results of the functional and morphological studies show that the causes of the attacks are pathological changes in the pons. Examinations excluded renovascular and endocrine causes of hypertension. Magnetic resonance imaging of the head found a malformation of blood vessels in the border edge infratentorially midbrain and pons. Electroencephalogram was normal several times.

Conclusion
Neurogenic hypertension was the result of vascular compression of the cranial nerves and brainstem and treatment with Bisoprolol and Tegretol led to a reduction in the frequency of attacks.

DOI: 10.1530/endoabs.32.P290
P291 Immobilisation hypercalcaemia in a young man
Gideon Mlawa1,2, Eswarri Chinnasamy1, Saiji Nageshwaran1 & Theofanoyiannis Panoyiati1
1Croydon University Hospital, London, UK; 2St Georges Hospital, London, UK.

Background
Immobilisation hypercalcaemia is serious complication of prolonged immobility of any cause such as spinal cord injury, polio victims, burns victims, as well as trauma patients.

Case
Eighteen-years old student was admitted to the hospital following road traffic accident. He sustained multiple fractures, skull, spine, chest and pelvis. He also sustained abdomen and pelvic haematoma. At scene of crash he had GCS 5/15, needing intubation and was airlifted to trauma centre, where he underwent extensive surgery laparotomy and pre-peritoneal packing, reduction of fracture dislocation of right, open reduction and fixation of bilateral pelvis fracture and acetabulum. His past medical includes orchidectomy after failed orchiectomy, and epistaxisis. After that he was transferred to his local Hospital for rehabilitation. His bloods showed Na+ 143, K 3.3, creatinine 45, calcium 3.0, PTH 0.9 pmol/l, 24 h urinary calcium 15.1 mmol/l vitamin D 46 phosphate 1.08, ALP 95, AST 45, Hb 12. He had normal calcium (2.25 mmol/l) during his initial admission to the trauma centre.

He was treated with i.v. fluids and pamidronate 30 mg single dose and his calcium level normalise. His calcium remains normal and the patient is undergoing physiotherapy.

Discussion
Immobilisation hypercalcaemia is a common complication of prolonged immobility of different causes including road traffic accident. Although well described among young patients with spinal cord it may happen in immobile patients following road traffic accident as demonstrated in our case report. It usually develops 1–16 weeks post trauma, and it may remain elevated up to 12 months.

Conclusion
Prolonged immobility following road traffic accident may cause hypercalcaemia which is reversible.

DOI: 10.1530/endoabs.32.P291

P292 Parathyroid carcinoma: an atypical case in a patient submitted to Bariatric surgery
Paula Sánchez Sobrino, Pablo A. Fernández Catalina & Carlos Alvarez Alvarez
Área de Xestión Integra da Pontevedra-Salnés, Pontevedra, Spain.

Background
Parathyroid carcinoma accounts for <1% of cases of primary hyperparathyroidism. Clinical presentation is usually related to severe hyperparathyroidism associated to elevated serum PTH (three times above the upper limit). These values are so much higher than in primary hyperparathyroidism due to a benign adenoma. Moreover, 30–75% of patients had a palpable neck mass.

Clinical case
Fifty-one-year-old female, submitted to bariatric surgery by a biliopancreatic diversion (Larrad’s technique) in 2002. He left treatment and follow-up at Nutrition Department. He is admitted to hospital because of an acute respiratory failure when a right cervical mass is discovered. TC showed a trachea deviation related to a 7 cm mass depending from the right thyroid lobe. FNA was suspicious for a follicular neoplasm with Hurthle cells. In previous analysis patient had many normal calcium values but some slightly elevated, chronic hypophosphatemia and very high intact PTH (values above 500 ng/ml, range 9–70). Surgery was performed including a total thyroidectomy, cervical exploration looking for any parathyroid adenoma and a tracheostomy. Histological study revealed a parathyroid carcinoma of 7.8 cm×4.6 cm×3.3 cm and one-gland hyperplasia. Patient developed a hungry bone syndrome with high needs of calcium and calcitriol. 25OHvitamin D was undetectable and post-surgical PTH was 178.5 pg/ml.

Conclusion
Main form of presentation of parathyroid carcinoma is severe hypercalcemia. However, our patient had a normocalcemic hyperparathyroidism. Absence of hypercalcemia despite of so high PTH is explained by a malabsortive bariatric procedure that excluded duodenum and first part of jejunum conditioning a chronic malabsorption of calcium and vitamin D.

DOI: 10.1530/endoabs.32.P292

P293 Autoimmune polyglandular syndrome type IV with twins pregnancy: clinical, diagnostic, evolutive aspects and treatment
Cristina Corina Pop Radu
University of Medicine and Pharmacy, Targu Mures, Romania.

Autoimmune polyglandular syndromes (APS) are characterized by the association of two or more endocrine and/or nonendocrine autoimmune diseases with different immunologic features of their pathogenesis.

Based on the clinical picture is divided into four different types. Type I APS comprises mucocutaneous candidiasis, hyperparathyroidism and Addison’s disease. Type II APS is defined by autoimmune Addison’s disease in association with chronic autoimmune thyroiditis and/or type one diabetes mellitus. Type III APS is composed of autoimmune thyroid diseases associated with other autoimmune conditions, excepting Addison’s disease. The rest of autoimmune combinations not included in the previous groups, belong to type IV APS.

We present a 40 years old woman who was diagnosed with chronic autoimmune thyroiditis and Addison’s disease four years ago, with subsequent development of hipoparathyroidism (possibly autoimmune mechanism?). At age 37, she became first time pregnant with twins. We discuss clinical, diagnostic, evolutive aspects and especially those of treatments during pregnancy, taking into consideration the number of co morbidities who requiring carefully medication with possible drug interactions and adverse effects.

DOI: 10.1530/endoabs.32.P293

P294 Hypercalcemia in patient five years after the diagnosis of gastrinoma
Urša Kekš & Miro Cokol
University Medical Center Maribor, Maribor, Slovenia.

Introduction
We diagnosed multiple endocrine neoplasia type 1 (MEN1) based upon the occurrence of two primary MEN1 tumor types in patient without family history of MEN1. Hyperparathyroidism was diagnosed in patient five years after gastrinoma surgery. With hormone tests and morphologic investigation we excluded pituitary adenoma.

Case report
Forty-nine year old patient was admitted with abdominal pain and vomiting. Laboratory testing revealed elevated values of calcium 3.29 mmol/l (normal range 2.2–2.6 mmol/l), ionized-calcium 1.88 mmol/l (1.12–1.23 mmol/l) and intact parathyroid hormone 365 ng/l (10–65 ng/l). We performed ultrasonography of neck region and subtraction thyroid scan. Investigations showed multiple parathyroid adenomas. The patient was referred to thoracic surgeon. Two years ago, he was diagnosed whit kidney stones and was not referred to endocrinologist. In 2007, he was diagnosed with gastrinoma. Tumor was located in pancreatic head, there was no metastatic disease. Whipple operation was performed. At that point we excluded the possibility of MEN1 with laboratory testing.

Discussion
MEN1 is heritable disorder characterized by a predisposition to parathyroid adenomas, anterior pituitary adenomas and tumors of pancreatic islet cells. Multiple parathyroid adenomas causing hyperparathyroidism are the most common manifestation of MEN1 with almost 100% penetrance and in the most cases the initial manifestation. Pancreatic islet cell and gastrointestinal adenomas become clinically apparent in one-third of patient, approximately 60% have Zollinger–Ellison syndrome (ZES). ZES is initial clinical manifestation of MEN1 in 40% of patient. On the other hand, MEN1 is present in 20–60% of patients with ZES. Pituitary disease occurred in 60% of patients.

DNA testing for MEN1 gene mutations is available and can provide valuable information in specific situation.

Conclusion
Anually monitoring and biochemical screening in all patients with diagnosed MEN1-associated tumors has to be considered.

DOI: 10.1530/endoabs.32.P294
**P295**

**Presence of Paget’s disease in a patient with endometrium carcinoma**

Ayse Kubat Uzum¹, Gulsah Yenidunya Yalin², Nurdan Gul³, Bulent Canbaz¹, Sema Ciftci Doganslan¹, Bilge Bilgic¹ & Nese Cakir Ozyel¹

¹Division of Endocrinology and Metabolism, Department of Internal Medicine, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey; ²Department of Pathology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey.

**Introduction**

Isolated bone metastasis of endometrium carcinoma is rare; but if it occurs, pelvis and vertebral are involved mostly. Co-existence of undiagnosed Paget’s disease in a patient with malignancy causes major problems in differential diagnosis.

**Case**

A 77-year-old woman was admitted to our hospital with severe pelvic pain. She had been diagnosed with inoperable endometrium adenocarcinoma for over a year. Metastatic bone disease was suspected because of pain localized to pelvic region. Sacroiliac graphy and computed tomography (CT) indicated lytic lesions on sacrum, pubic ischiadium and L5 vertebra. Increased uptake was evident in bone scintigram (Tc99). These lesions were reported as metastatic bone involvement. However, Paget’s disease was also considered in differential diagnosis.

In (18)F-fluorodeoxyglucose positron emission tomography/CT (18) F-FDG PET/CT, osteolytic and osteosclerotic lesion areas showed heterogeneous FDG uptake in early (SUV max:7.4) and late images (SUV max:8.7). Also fused images showed moderate FDG uptake on osteosclerotic lesions (SUV max:3.7) which may be compatible with Paget’s disease. She was referred to Endocrinology Department with a suspect of Paget’s disease. Bone biopsy, which was performed to exclude metastatic carcinoma revealed osteoblastic and osteoclastic activity in trabecular bone attributable to Paget’s disease and no focus of tumor infiltration was evident. Laboratory evaluations were as follows: BUN:24 mg/dl (n: 8-22 mg/dl), creatinine: 2.3 mg/dl (n: 0.7-1.4 mg/dl), serum corrected calcium: 9.6 mg/dl, PTH: 80 pg/ml (n: 10-55 pg/ml), β-CALL: 1.2 g/ml (<1 g/ml) ALP: 120 UI (n: 35-105 UI) Callotinin (s.c.) was applied to control the disease as the patient’s glomerular filtration rate was 24.3 ml/min per 1.73 m².

**Conclusion**

Our patient had active disease and showed low-moderate uptake (lower than expected in malignant disease). If osteoblastic and osteoclastic activity of Paget’s disease is associated with increased glycolysis and glucose use, it could cause false-positive uptake of (18)F-FDG in PET studies. Paget’s disease should be considered in differential diagnosis of positive bone scintigraphy finding during screening for bone metastasis.

DOI: 10.1530/endoabs.32.P295

---

**P297**

**Primary hyperparathyroidism associated with atrial septal defect, interatrial septal aneurysm and skeletal anomaly: a case report**

Fatma Neslihan Cuhaci¹, Setlika Burak Polat¹, Berna Evranos², Telat Kales³, Reyhan Erosy³ & Bekir Cakir³

¹Department of Endocrinology and Metabolism, Ataturk Education and Research Hospital, Ankara, Turkey; ²Department of Endocrinology and Metabolism, Yildirim Beyazit University, Ankara, Turkey; ³Department of Cardiology, Yildirim Beyazit University, Ankara, Turkey.

The classic clinic manifestation of primary hyperparathyroidism (PHPT) is osteitis fibrosa cystica, a severe skeletal disease characterized by brown tumors, bone cysts and deformities, due to extremely elevated bone resorption elicited by continuously high parathyroid hormone (PTH) levels. In cardiovascular system there may be shortened QT interval, deposition of calcium in heart valves, coronary arteries, and myocardial fibers. Here, we report a case with PHPT, who have anorexia nervosa, skeletal anomaly, atrial septal defect (ASD) and interatrial septal aneurysm.

**Case report**

An 18-year-old woman, who has anorexia nervosa has applied for constipation. She had bradycardia, low weight (BMI: 15 kg/m²), and prognathism. The radiographic finding of the extremities showed that, bilaterally 2 and 5 metacarpals were short in the hands, and bilaterally 1, 3, 4, 5 metatarsals in the feet were short. Laboratory tests revealed hypercalcaemia, hypophosphatemia and hyperparathyroidism. Her 24-h urinary calcium was 504 mg/day. The neck ultrasound revealed a 4.9×6.8×10.4 mm hypoechoic lesion in the outside the thyroid right lobe inferior. Sestamibi scintigraphy results were consistent with parathyroid adenoma. Renal ultrasonography determined millimetric crystaloads in the right kidney. Bone mineral densitometry revealed osteopenia. Her electrocardiography showed a shortened QT interval and bradycardia. Echography revealed an ASD and interatrial septal aneurysm. Her pituitary hormonal levels were consistent with panhypopituitarism. She had also evaluated for the eye, ear and nose anomaly, but no pathology was found. After the diagnosis and emergency treatment for hypercalcaemia she had underwent parathyroidectomy. Postoperative her calcium and parathyroid levels were reduced in normal levels.

Our case revealed hypercalcaemia and hyperparathyroidism and also unusual manifestations like anorexia, ASD, interatrial septal aneurysm and skeletal anomaly. In literature to our knowledge, there is only one case with PHPT and ASD associated with mongoloid features. In conclusion, the patients with PHPT may be evaluated for atypical manifestations of cardiac and skeletal system.

DOI: 10.1530/endoabs.32.P297

---

**P298**

**Hypercalciuria in a patient with central diabetes insipidus**

Alexandros Ginis¹ & Ifigenia Kostoglou-Athanassiou²

¹Endocrinologist, Athens, Greece; ²Department of Endocrinology, Red Cross Hospital, Athens, Greece.

Central diabetes insipidus is characterized by increased water excretion which is corrected by the administration of antidiuretic hormone. Hypercalciuria is known to be associated with osteoporosis. The aim was to describe the case of a patient with central diabetes insipidus, hypercalcemia, vitamin D deficiency and severe osteoporosis.

The case of a patient, female aged 64 years, presenting with central diabetes insipidus, hypercalcemia, vitamin D deficiency and severe osteoporosis is described. The patient suffered from central diabetes insipidus since the age of 20 years. Laboratory investigations revealed severe hypercalcaemia, urine calcium levels being 800 mg/24 h, decreased blood calcium and vitamin D deficiency, 25(OH)D levels being 10 mg/ml (normal levels >30 mg/ml). PTH levels were increased and T score was –4. Vitamin D was administered along with a thiazide diuretic for the correction of vitamin D deficiency and hypercalciuria. Vitamin D levels increased and hypercalciuria was partially corrected. Sequentially, strontium ranelate was administered without an improvement in bone density. Strontium ranelate was stopped, alendronate was administered and bone mineral density increased.

**Conclusions**

The extremely rare case of a patient with central diabetes insipidus, hypercalcemia, vitamin D deficiency and severe osteoporosis is described. Hypercalciuria was partially resistant to thiazide therapy as well as osteoporosis to strontium ranelate, finally improving with bisphosphonates. The coexistence of hypercalciuria, salt losing nephropathy and renal diabetes insipidus has been described in the context of glomerular disease. Osteoporosis in the context of central diabetes insipidus has also been described, responding to bisphosphonates.
However, the coexistence of central diabetes insipidus with hypercalciuria and severe osteoporosis is extremely rare.

DOI: 10.1530/endoabs.32.P298

P299

A recurrent case of subacute thyroiditis improved with the onset of pregnancy
Taner Bayraktaroglu1,2, Fatih Kuzu1,3, Yavuz Sami Salihoglu2,3, Muammer Bilici2, Sevil Ugyun Ilkihan1 & Mehmet Ibrahim Harma4
1Division of Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine, Bulent Ecevit University, Zonguldak, Turkey; 2Department of Nuclear Medicine, Faculty of Medicine, Bulent Ecevit University, Zonguldak, Turkey; 3Department of Internal Medicine, Endocrinology and Diabetology, General and Visceral Surgery, Klinikum Bielefeld Mitte, Bielefeld, NRW, Germany; 4Faculty of Medicine, Bulent Ecevit University, Zonguldak, Turkey.

Introduction
Thyroid disorders such as subacute thyroiditis occur rarely in pregnancy. We report a recurrent case of subacute thyroiditis improved with the onset of pregnancy.

Case report
A 32-year-old Turkish woman who requested pregnancy and planned insemination was referred due to malaise and neck pain in the left side a week ago. She was presented with low-grade fever, fatigue, pharyngitis symptoms, neck pain and extremely tenderness in the right side of thyroid about four months ago. Subacute thyroiditis was diagnosed with colour doppler sonography of thyroid showed decreased vascularise and flow in the thyroid and elevated markers of inflammation. Owing to increasing symptoms and signs, glucocorticoid therapy was given. Three months after discontinuation of steroid therapy with relief, she was admitted to the other side neck pain and tenderness during the induction of ovulation. Her symptoms, signs and inflammatory parameters were progressed. Hence, steroid therapy was given a short course to the patient on five days before insemination. It is discontinued before the day of insemination. During first month of pregnancy, the clinic situation was resolved, and improved without need for medications. Because of hypothyroidism, levothyroxine was given throughout pregnancy.

Conclusions
Subacute thyroiditis is rare and an important disorder during pregnancy. The beginning of pregnancy, physiological and immunological mechanisms may be responsible for the recovery of subacute thyroiditis.

DOI: 10.1530/endoabs.32.P299

P300

High rate of malignant disorders in patients with primary hyperparathyroidism
Stanley Kirana1, Bettina Eggert1, Kirsten Oberwelland2, Guido Schüermann2 & Joachim Feldkamp1
1Department of Internal Medicine, Endocrinology and Diabetology, Klinikum Bielefeld Mitte, Bielefeld, NRW, Germany; 2Department of General and Visceral Surgery, Klinikum Bielefeld Mitte, Bielefeld, NRW, Germany.

Introduction
Some new data suggest a coincidence of differentiated thyroid carcinoma in patients with primary hyperparathyroidism (PHPT).

Methods & design
We performed a retrospective analysis of our patients (n = 267) with primary hyperparathyroidism from 2007 until 2011.

Results
Musculoskeletal pain was reported by 34.2% of the patients. Gastrointestinal discomfort was complained by 28.8%, and 21.1% had nephrolithiasis. Out of 267 patients, 223 patients (174 women, 49 men) underwent parathyroidectomy. Forty-four patients received conservative therapy. In 223 patients ultrasound examination showed uniodular goiter in 38 patients (14.8%) and multinodular goiter was found in 117 patients (45.5%). After surgery, histological specimens from thyroid glands revealed differentiated thyroid cancer in 17 patients (7.62%). Follicular thyroid cancer was seen in two patients (0.90%), papillary thyroid cancer in 14 patients (6.27%), and medullary thyroid carcinoma in one patient (0.45%). Eight patients had C-cell hyperplasia. Including the history of other malignant diseases, 26.1% of the patients had an oncologic disease. Of 223 patients, only 25 patients (11.2%) had no other disease than PHPT. Ninety-one patients (40.8%) suffered from endocrine diseases: multiple endocrine neoplasia type 1 (11 (4.93%), Hashimoto’s thyroiditis: 42 (18.8%), Grave’s disease: 1 (0.45%), Diabetes mellitus type 1 and type 2: 13 (5.8%), polyglandular autoimmune syndrome: 1 (0.5%). One hundred and seventy-four patients (78%) suffered from cardiovascular disease (mostly arterial hypertension), renal disease was found in 66 patients (29.6%) and 81 patients (36.3%) had gastrointestinal disease.

Conclusion
Thyroid cancer is not rare in patients with PHPT. Many of the patients have a history of other malignant diseases. Hashimoto’s thyroiditis is a frequent thyroid disease in this group of patients. It still has to be investigated, if there is a causal relationship between malignancy and hyperparathyroidism.

DOI: 10.1530/endoabs.32.P300

P301

Experience in the use of Tolvaptan in elderly patients with significant hypotonia
Agnieszka Swiecicka, Rahul Nayar & Ashwin Joshi
Sunderland Royal Infirmary, Sunderland, UK.

Introduction
Tolvaptan is an oral vasopressin V1 receptor antagonist which offers a novel treatment for euvoletic and hypervolaemic hyponatraemia. Here, we report our experience with Tolvaptan in elderly patients.

Case 1
Seventy six-year-old lady with background of hyperthyroidism, hypertension and alcohol excess presented with acute onset of confusion. Her admission Sodium [Na+] level was 117 mmol/l and represented an acute drop from normal level after a thiazide diuretic was introduced two days earlier. Acute thyroid dysfunction and adrenal insufficiency were excluded. Despite stopping bendroflumethiazide, [Na+] fell further to 108 mmol/l 48 h later. Urinary spot [Na+] was 29 mmol/l and urine osmolality 766 mOsm/kg in the context of euvoletaemia. Following administration of 15 mg of Tolvaptan, [Na+] rose to 117 mmol/l on day one and 122 mmol/l on day 2. Tolvaptan was discontinued and hyponatraemia improved on fluid restriction only with [Na+] level 132 mmol/l 48 h later.

Case 2
Ninety one-year-old lady with known congestive cardiac failure and hypertension was admitted with a fall. She was known to have mild hyponaetaemia, secondary to loop diuretic use. [Na+] level fell rapidly from 130 to 115 mmol/l a week post admission and continued to decline despite withholding the diuretic and ACEI, fluid restriction and Demeclocycline use (300 mg 6 hourly). Plasma osmolality was low at 245 mOsm/kg with urine osmolality at 958 mOsm/kg. Thyroid dysfunction and hypocortisoloselamia were excluded. Tolvaptan 15 mg was introduced at [Na+] level of 106 mmol/l and resulted in gradual improvement in hyponatraemia with [Na+] level at 111 mmol/l on day 1, 118 mmol/l on day 2 and 127 mmol/l on day 3 post Tolvaptan. The medication was discontinued and a [Na+] level remained stable on fluid restriction.

Conclusion
Tolvaptan is a safe and effective treatment of hyponatraemia in elderly population providing more prompt rise in serum sodium than fluid restriction and Demeclocycline.

DOI: 10.1530/endoabs.32.P301

P302

Hypercalcemia secondary to concomitant thyrotoxicosis and B cell lymphoma
Liu Yuan, Gabriel Cher, Wei Feng Lee, Weiliang Abel Chen, Shang Ming Samuel Lee, Seew Cheng Jye & Alvin Wai Kit Tan
Tan Tock Seng Hospital, Singapore, Singapore.

Introduction
Mild hypercalcemia can present in 10–15% of hyperthyroid patients. In contrast, its incidence in B cell lymphoma is considerably less (7–8%) but its levels are much higher. We report a patient with hypercalcemia secondary to both thyrotoxicosis and lymphoma.

Case report
A 55 year-old lady presented with non specific symptoms of appetite loss and lower limb weakness. Comorbidities included hypertension, diabetes mellitus, hyperlipidaemia and a previous history of consumption of traditional herbal supplements. Examination was unremarkable except for bilateral hand tremors.

DOI: 10.1530/endoabs.32.P302

Endocrine Abstracts (2013) Vol 32
There was no hepatosplenomegaly or lymphadenopathy. Laboratory results: Ca(adj) 3.59 mmol/l (RI: 2.15–2.58), PO4 1.2 mmol/l (RI: 0.8–1.6), PTH<0.6 pmol/l, 25(OH)D 19 ng/l (RI: 30–50), T3 67 pmol/l (RI: 8–21), TSH 0.03 mIU/l (RI: 0.34–5.6), TRAb 7.5 IU/l. A normal short synacthen test excluded concomitant hypocortisolism. A presumptive diagnosis of PTH-independent hypercalcaemia due to thyrotoxicosis was made. A dose of pamidronate normalised the calcium levels but despite treatment with anti-thyroid medications, hypercalcaemia rapidly returned. A search for malignancy revealed elevated LDH and beta2 microglobulin and multiple lymphadenopathy on abdominal imaging. This was followed up with a bone marrow examination showing B cell lymphoma. She was subsequently referred to hematology for chemotherapy.

Conclusion
Despite the presence of a known cause of hypercalcaemia, malignancy must always be extensively investigated for and excluded when calcium levels are markedly elevated. Hypercalcaemia in B-cell lymphoma is not uncommon and carries a poorer prognosis, thus it is crucial that diagnosis be suspected and made early so that appropriate treatment can be carried out.

DOI: 10.1530/endoabs.32.P302

P303 Hyperthyroidism-induced heart block: a case series in the Philippine general hospital
Anthony Harvey Aguilar & Mark Anthony Sandoval
Philippine General Hospital, Manila, The Philippines.

Cardiac arrhythmias in thyrotoxicosis are usually seen as sinus tachycardia and atrial fibrillation but conduction abnormalities in the form of heart blocks do occur in rare instances. We present here four hyperthyroid patients with complete heart blocks. Cases 1 and 2 are young women diagnosed with Graves’ disease who both experienced syncpe and were seen to have 3rd degree atrio-ventricular block. Case 3 is a young woman who presented with palpitations, fever and shortness of breath. Her 12 lead ECG showed diffuse ST-segment elevation consistent with pericarditis and complete heart block. Case 4 is a young male with enlarged anterior neck mass and hyperthyroid symptoms who was not cleared for thyroideectomy due to 3rd degree AV block. Development of conduction problems in hyperthyroidism can be due to overwhelming thyroid hormones per se and contributed by acute infections, use of rate control drugs, electrolyte imbalances, and cardiac anomalies. Resolution of clinical, electrophysiological, and biochemical abnormalities occurred in our patients after achieving euthyroidism.

DOI: 10.1530/endoabs.32.P303

P304 A case with thyroid acropachy as the initial manifestation of thyrotoxicosis
Serpi Bal1, Pelin Tütüncüoglu2, Emel Atar1, Nese Olmez Sariyay1, Ozlem Yoleri1, Bengi Oz1, Hikmet Kocyigit1 & Ece Harman2
1Department of Physical Medicine and Rehabilitation, Ataturk Training and Research Hospital, Izmir, Turkey; 2Department of Endocrinology, Ataturk Training and Research Hospital, Izmir, Turkey.

Thyroid acropachy is an uncommon and usually late complication of thyroid disease. The typical clinical presentation of thyroid acropachy includes clubbing, distal soft tissue swelling and periостеal reaction involving the tubular bones of the hands and feet. It is usually associated with exophthalmos and thyroid dermopathy. We present a case with thyroid acropachy as an initial manifestation of toxic adenoma.

A 69-year-old man was admitted to our out-patient clinic with complaints of pain and swelling in his hands and wrists. These symptoms had been present for 3 years. His physical examination revealed clubbing of the fingers of both hands and exophthalmos. Dermopathy was not observed in our patient. Radiographs of both hands revealed periostеal reaction that was bilateral and symmetrical involving all proximal phalanges. Laboratory investigation showed elevated serum T4, depressed TSH levels. Serum T3 and alkaline phosphatase levels were in normal range. Thyroid scintigraphy demonstrated a toxic adenoma in the right lobe of thyroid gland. The patient was diagnosed as thyrotoxicosis with thyroid acropachy and medical treatment was initiated involving antithyroid drugs and low dose steroid.

We present this case with thyroid acropachy as an unusual initial presentation of thyrotoxicosis.

DOI: 10.1530/endoabs.32.P304

P306 Adefovir dipivoxil-induced acquired Fanconi’s syndrome presenting as hypokalemia
Shang Ming Samuel Lee, Cheng Jye Seow & Melvin Khee-Shing Leow1
1Tan Tock Seng Hospital, Singapore, Singapore; Ministry of Health Holdings, Singapore, Singapore.

Introduction
Adefovir, commonly used for the treatment of hepatitis B, has dose-related nephrotoxicity, especially at doses of 60 mg daily and above. We describe a patient with Fanconi’s syndrome after being on low dose adefovir for more than 5 years.

Case report
A 62-year-old Chinese man, a chronic carrier of Hepatitis B on adefovir 10 mg daily for over 5 years, presented with the incidental finding of profound yet asymptomatic hypokalemia (K 1.9 mmol/l, RI: 3.5–5.0 mmol/l). There were no
previous plasma electrolyte screens. He had weight loss, fatigue and bone pain for months. A high trans-tubular potassium gradient suggested renal potassium wasting. In addition, there was an associated non-anion gap metabolic acidosis, hyperphosphatemia of 0.4 mmol/l (RI: 0.8–1.6 mmol/l) and hypouricemia of 154 μmol/l (RI: 250–550 μmol/l). The fractional excretion of phosphate was raised (59%, RI: 5–20%). The 24 h urine uric acid was 2778 μmol/day (RI: 500–5800 μmol/day) which was inappropriately normal. Urine protein excretion (24 h urinary total protein 0.880 g/day) and urinary amino acids were also raised, and glucose urinary dipstick was positive (2 +). Dual energy X-ray absorptionmetry showed osteoporosis. A diagnosis of acquired Fanconi’s syndrome secondary to adefovir was made. Upon substitution with entecavir, we expect resolution of the electrolyte abnormalities to occur over the next few months.

Conclusion

It has been shown that adefovir depletes mitochondrial DNA which contributes mechanistically to proximal tubular dysfunction and hence acquired Fanconi’s syndrome. Patients on adefovir therapy should therefore be screened periodically for electrolyte abnormalities, even when used at low doses.

P308

Graves’ disease associated with severe hypoalbuminemia

Hacer Şen, Emine Binnetoğlu, Mehmet Aşık, Fahri Güney, Erdem Akbal & Neslihan Bozkurt
Deparment of Internal Medicine, Medical Faculty, Çanakkale Onsekiz Mart University, Çanakkale, Turkey.

Introduction

The most common cause of thyrotoxicosis is Graves’ disease. Thyroid storm mostly presents with fever, tachycardia, arthralgia, jaundice, congestive heart failure and consciousness. We report a rare case of severe hypoalbuminemia with thyroid storm. To our knowledge it is the first case of severe hypoalbuminemia due to thyrotoxicosis in literature.

Case

Forty one years old female had been followed up with the diagnosis of Graves’ disease for 14 years. She was admitted with palpitations, shortness of breath, mild abdominal pain, nausea and complaints of discomfort. On examination, she had a temperature of 38.3 °C, arterial blood pressure 178/88 mmHg, irregular heart rate of 140 beats/min, respiratory rate of 22 breaths/min, mild pretibial edema and was seen nervous. Blood analysis revealed TSH of 0.005 IU/ml, FT₃ of 10.9 pg/ml, FT₄ of 3.5 pg/ml ALT: 16 U/l, AST: 23 U/l, total-protein: 4.7 g/dl, albumin: 1.8 g/dl. Propylthiouracil, propranolol, Lugol’s solution and dexamethasone were started. On the fourth day of treatment, TSH of 0.005 IU/ml, FT₃ of 2.97 pg/ml, FT₄ of 1.98 pg/ml. Total thyroidectomy was performed. Other underlying factors for hypoalbuminemia were excluded. In the follow-up, total protein and albumin levels returned to normal limits.

Conclusion

Severe hypoalbuminemia, that can be seen in many serious diseases, may be encountered in the long term progress of thyrotoxicosis unexpectedly. Hypoalbuminemia should be evaluated during thyrotoxicosis.

DOI: 10.1530/endoabs.32.P308

P310

Challenges in the management of hypogonadotropic hypogonadism

Cheng Jye Seow, Liu Yuan Gabriel Cher, Shang Ming Samuel Lee, Wei Liang Abel Chen, Wei Feng Lee, Alvin Wai Kit Tan &Shaikh Abdul Kader Kamaldeen Abdal Shakoor
Tan Tock Seng Hospital, Singapore, Singapore.

Introduction

One of the main challenges in the management of male hypogonadotropic hypogonadism (HH) is in the restoration of fertility. We describe 2 patients with...
The normal sperm count is attained post gonadotropin treatment. The cost of testicular size/normalisation of serum testosterone, azoospermia persisted in the male. Despite the presence of good prognostic features such as improvement in fertility, no secondary sexual characteristics eventually developed. Learning point: The urinary HCG 6.1 fmol/mgCr was within normal range in benign hyperparathyroidism whose diagnosis is very challenging. Therefore, our objective was to differentiate between benign and malignant hyperparathyroidism on the basis of excretion of HCG and its malignant isoforms in urine.

Background
Parathyroid carcinoma is a rare endocrine malignant neoplasm resulting from the parenchymal cells of the parathyroid glands and infrequent cause of primary hyperparathyroidism whose diagnosis is very challenging. Therefore, our objective was to differentiate between benign and malignant hyperparathyroidism on the basis of excretion of HCG and its malignant isoforms in urine.

Materials and methods
It was a hospital based study carried out using data retrieved from the register maintained in Manipal Teaching Hospital from 1st January, 2008 and 31st August, 2012. The variables collected were urinary HCG, urinary HCG malignant isoform, calcium, parathyroid hormone. All these biochemical parameters were analyzed in the Central Laboratory of our hospital by standard and validated methods.

Results
The urinary HCG 6.1 ± 6 fmol/mgCr was within normal range in benign hyperthyroidism. The urinary HCG was markedly high in three cases of malignant hyperparathyroidism. The maximum value of excretion in urine for HCG was 2523 fmol/mgCr. The excretion of malignant isoform of HCG in urine was 0 in benign hyperparathyroidism and in four cases of malignant hyperparathyroidism which falls in category of persistently low HCG. The maximum excretion of malignant isoform of HCG in urine was 1.8 which falls in category of markedly high HCG.

Conclusion
The elevated expression of standard or hyperglycosylated HCG is an adverse category of markedly high HCG. The elevated expression of standard or hyperglycosylated HCG is an adverse category of markedly high HCG. The elevated expression of standard or hyperglycosylated HCG is an adverse category of markedly high HCG. The elevated expression of standard or hyperglycosylated HCG is an adverse category of markedly high HCG.

Carlos Haya Hospital, Málaga, Spain.

Objective
To report a case of hyperandrogenism attributable to the presence of an ovarian Leydig cell tumor secreting testosterone in a postmenopausal woman.

Methods
The laboratory, radiologic, and pathologic findings in our case are described.

Results
A 59-year-old woman presented with a history of gradual increase in facial and body hair, scalp hair loss, male pattern baldness, and deepening of her voice, beginning 5–6 years before. She had two normal pregnancies and spontaneous menopause at age 47 years. She had hypertension and hyperlipidemia. Laboratory tests showed elevated levels of total testosterone (575 ng/dl), very low gonadotrophin levels and normal levels of 17-OH-Pg. Androstenedione and DHEA-S. Her high level of testosterone was not suppressed with dexamethasone. Ultrasound study and abdominal computed tomographic scan showed the adrenal glands to be normal in size. Transvaginal ultrasonography revealed no tumor. Bilateral oophorectomy was performed, and an ovarian Leydig cell tumor in left ovary was diagnosed, in the contralateral ovary a stromal hyperplasia was found (non-neoplastic condition of the ovary also associated with clinical manifestations of hyperandrogenism from ovarian production of male hormones). The postoperative serum testosterone level returned to normal and the patient showed a complete regression of clinical symptoms after the surgical intervention.

Conclusion
Our case illustrates that a virilizing ovarian tumor can be small and elude imaging studies, but may be detected by means of well-considered clinical management. And, particularly in our case, we found a Leydig cell tumor and a contralateral stromal hyperplasia.

DOI: 10.1530/endoabs.32.P312
Follicular thyroid cancer with functioning lung metastasis
Queenie Ngabob, Ruben Ogbaa & Myrna Buenaluz-Sedurante
1Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, Philippine General Hospital, University of the Philippines, Manila, The Philippines; 2Section of Nuclear Medicine, Department of Medicine, Philippine General Hospital, University of the Philippines, Manila, The Philippines.

Background
Functioning metastasis from a primary thyroid cancer is exceedingly rare. Failure to proceed to hypothyroidism after total thyroidectomy denotes remaining hormone production from functioning metastasis. Radioactive iodine ablation will ablate these remaining tissues. We present the case of a patient with follicular thyroid cancer, lung metastasis and detectable thyroid hormones after thyroidectomy.

Clinical presentation
The patient is a 71-year-old Filipina who had recurrent thyroid nodules for the past 22 years. She underwent four surgeries and the most recent was completion thyroidectomy for a 6.7 x 6.4 x 5.5 cm lobulated mass in the left thyroid bed. Preoperative TSH suppressed at 0.008 mIU/l (NV: 0.3–3.8) and free thyroxine was elevated at 36.2 pmol/l (NV: 11–24). Thyroid scintigraphy using 6 mCi of technetium 99m pertechnetate showed functioning thyroid tissue with a conglomerate size of 8 x 5.6 cm. Chest CT scan revealed numerous small well-defined nodules scattered in both lungs. She was treated with Methimazole 20 mg daily for 4 weeks prior to surgery. Histopathology revealed follicular carcinoma in the left thyroid lobe, the strap muscles and cervical lymph nodes. Three months after thyroidectomy, her TSH remained suppressed at 0.2 mIU/l and fT4 detectable at 11.7 pmol/l. Diagnostic whole body scan using 3 mCi Iodine-131 showed two small foci of functioning thyroid remnant measuring 1.6 x 1.0 cm and 0.6 x 0.6 cm. Both lungs showed increased tracer uptake. A diagnosis of functioning lung metastasis was made. The patient underwent radioactive iodine ablation with 150 mCi of Iodine-131. Thyroid function tests done one month later revealed an elevated TSH 33.4 mIU/l and low fT4 at 8.2 pmol/l indicative of successful ablation of functioning thyroid tissue.

P316 Mixed medullary-follicular carcinoma of the thyroid: two case reports
Alper Celil Ushugullari, Eda Demir Onal, Serdar Balci, Reyhan Ersoy & Bekir Cakir
1Department of Endocrinology and Metabolism Diseases Department, Ankara Ataturk Education and Research Hospital, Yildirim Beyazit University, Ankara, Turkey; 2Pathology Department, Ankara Ataturk Education and Research Hospital, Yildirim Beyazit University, Ankara, Turkey.

Mixed medullary-follicular carcinomas (MMFC) of the thyroid are rare tumors which presents <0.15% of all thyroid tumors showing the morphological and immunochemical properties of both parafollicular and follicular cell lineages. Cases were immunoreactive for both calcitonin and thyroglobulin.

Case 1
A 28-year-old female patient referred us for evaluation of a thyroid mass located on the left lobe. Ultrasonography (US) revealed 38 mm solid isoechoic nodule with well-defined margins on the left lobe. An US-guided fine needle aspiration (FNA) was performed and reported as follicular neoplasm. A total thyroidectomy with central lymph node dissection was performed. Immunostaining revealed that the tumor cells were diffusely positive for calcitonin and chromogranin. Further, there were scattered follicles that stained positively with antibody against thyroglobulin. The histological findings in correlation with the immunoprofile, support a diagnosis of MMFC. Post-operatively calcitonin level was 2.69 pg/ml. Radioactive iodine ablation with 150 mCi and l-thyroxine supression therapy had given to the patient.

Case 2
A 46-year-old female patient admitted with enlargement of a neck mass. US revealed 33 mm solid isoechocic nodule with ill-defined margins and microcalcifications on the left lobe of thyroid. US-guided FNA was reported as thyroid neoplasm with differentiation or anaplastic transformation. Patient’s serum level of calcitonin was 1802 pg/ml (normal <12 pg/ml). Results of blood testing for pheochromocytoma and hyperparathyroidism were within the normal range. Total thyroidectomy with central lymph node dissection was performed. The histological findings were consistent with MMFC with metastatic lymph nodes. The serum calcitonin level dropped to 3.75 pg/ml following the surgery.

Conclusion
The majority of MMFC occurs in a sporadic form, rarely it can be a component of MEN type 2. MMFC, medullary and follicular thyroid cancer behave differently in terms of clinical course and management. Identification of MMFC by FNA may be difficult, the proper immunostaining panel could have showed the different aspects of the mixed tumor.

Cyclosporine induced autoimmune thyroid disease: presentation of two cases
Eda Demir Onal, Alper Celil Ushugullari, Dilek Karayaka Arpaci, Rifki Ucler, Reyhan Ersoy & Bekir Cakir
Endocrinology and Metabolism Diseases Department, Ankara Ataturk Education and Research Hospital, Yildirim Beyazit University, Ankara, Turkey.

Immune suppressive patients due to any cause (disease, medication, etc.) rarely have autoimmune diseases. In this presentation, two patients diagnosed with Graves’ disease and subacute thyroiditis while taking cyclosporine therapy will be discussed.

Case 1
A 47-year-old female patient applied with weight loss, sweating and tremor. She had been on cyclosporine therapy for 3 years because of hypoplastic anemia. In laboratory tests; TSH: 0.005 uIU/ml (0.27–4.2), fT4: 2.77 ng/dl (0.9–1.7), and fT3: 28.56 pg/ml (1.8–4.6). Anti-TPO, Anti-TG and TSH receptor antibodies were positive. Ultrasound revealed enlarged thyroid gland with diffuse parenchymal heterogeneity. Thyroid scan showed increased uptake, which was diffuse and homogeneous in pattern. On radioiodine uptake test; 4th hour uptake was 46% (15–25%) and 24th hour uptake was 27% (25–35%). The patient was diagnosed as Graves’ disease. With thymoxidel therapy euthyroid state was achieved.

Case 2
A 41-year-old female patient admitted with pain and tenderness in the thyroid area. She had been using cyclosporine during the last 2 year period for psoriasis. In laboratory tests; TSH: 0.015 uIU/ml, fT4: 1.48 ng/dl, and fT3: 3.92 pg/ml. Anti-TPO and TSH antibodies were negative while anti-TG antibodies were positive. Ultrasonography showed multiple hypoechogenic thyroid nodules with ill-defined margins on the basis of chronic thyroiditis. In the thyroid scan there were

P315 Wegener’s granulomatosis in a patient with vitamin D deficiency
Panagiotis Athanassiou, Ifigenia Kostoglou-Athanassiou, Eleni Xanthakou, Anna Papadaki & Dimitra Basdragianni
1Department of Rheumatology, St Paul’s Hospital, Thessaloniki, Greece; 2Department of Endocrinology, Red Cross Hospital, Athens, Greece; 3Endocrinologist, Athens, Greece.

Wegener’s granulomatosis is characterized by necrotizing granulomatous vasculitis. It occurs initially in a localized form, disseminates in various degrees and particularly involves the respiratory tract and kidneys. It is an ANCA-associated vasculitis, a systemic disease of autoimmune aetiology. Recently vitamin D deficiency has been associated with the development of autoimmunity. The aim was to present a case of Wegener’s granulomatosis in a patient with vitamin D deficiency induced by gastric surgery for the treatment of morbid obesity.

A patient, female aged 47 years, presented with chronic episcleritis, conjunctivitis, retroorbital pain and erythema of the left eye over the course of 2 years. The patient had gastric surgery for the treatment of morbid obesity and had also been subjected to thyroideectomy for the treatment of a thyroid nodule. On clinical examination she had a hemorrhagic rash over the lower extremities and bilateral hearing loss.

Laboratory investigations revealed vitamin D deficiency, 25(OH)D3 levels being 11.7 ng/ml (normal levels >30 ng/ml), microscopic hematuria, proteinuria, and positive c-ANCA. Imaging studies revealed the presence of nodules in the lungs and signs of central orbital involvement. The diagnosis of Wegener’s granulomatosis was made. 1v methylprednisolone pulse therapy was initiated and vitamin D was administered orally with subsequent sustained improvement.

In conclusion, the case of a patient with Wegener’s granulomatosis and vitamin D deficiency after gastric surgery for morbid obesity is presented. Vitamin D deficiency is known to be associated with the development of systemic autoimmune diseases such as multiple sclerosis and rheumatoid arthritis. Vitamin D deficiency induced by gastric surgery may be implicated in the pathogenesis of a systemic autoimmune disease with ocular manifestations in this patient.

P317 Immune suppressive patients due to any cause (disease, medication, etc.) rarely have autoimmune diseases. In this presentation, two patients diagnosed with Graves’ disease and subacute thyroiditis while taking cyclosporine therapy will be discussed.

Case 1
A 47-year-old female patient applied with weight loss, sweating and tremor. She had been on cyclosporine therapy for 3 years because of hypoplastic anemia. In laboratory tests; TSH: 0.005 uIU/ml (0.27–4.2), fT4: 2.77 ng/dl (0.9–1.7), and fT3: 28.56 pg/ml (1.8–4.6). Anti-TPO, Anti-TG and TSH receptor antibodies were positive. Ultrasound revealed enlarged thyroid gland with diffuse parenchymal heterogeneity. Thyroid scan showed increased uptake, which was diffuse and homogeneous in pattern. On radioiodine uptake test; 4th hour uptake was 46% (15–25%) and 24th hour uptake was 27% (25–35%). The patient was diagnosed as Graves’ disease. With thymoxidel therapy euthyroid state was achieved.

Case 2
A 41-year-old female patient admitted with pain and tenderness in the thyroid area. She had been using cyclosporine during the last 2 year period for psoriasis. In laboratory tests; TSH: 0.015 uIU/ml, fT4: 1.48 ng/dl, and fT3: 3.92 pg/ml. Anti-TPO and TSH antibodies were negative while anti-TG antibodies were positive. Ultrasonography showed multiple hypoechogenic thyroid nodules with ill-defined margins on the basis of chronic thyroiditis. In the thyroid scan there were
suppressed areas in nodular pattern and a global nonhomogenous uptake. There was low radiodine uptake in the radiodine uptake test. The patient was diagnosed as subacute thyroiditis. Nonsteroidal anti-inflammatory drug and beta blocker were given. One month later, her thyroid function tests were within normal limits.

Conclusion
Cyclosporine rarely can be a cause of autoimmune disease by an unknown mechanism of abnormal modulation of the immune system. Patients taking cyclosporine especially those having another autoimmune disease or family history of thyroid disease must be carefully monitored with thyroid function tests.

DOI: 10.1530/endoabs.32.P317

P318

Never too late to discover some extra thyroid tissue
Ana Wessling1, Jose Maria Aragüez2,3, Flórebela Ferreira1 & Isabel Carmo1,2
1Endocrinology Department of Santa Maria University Hospital, Lisbon, Portugal; 2Faculty of Medicine, University of Lisbon, Lisbon, Portugal.

Introduction
Ectopic thyroid is a rare entity, resulting from developmental defects at early stages of thyroid embryogenesis. It’s prevalence is 1/100 000–300 000 in general population and 1/4000–8000 in patients with thyroid disease. This condition is more common in females, in Asians and may occur at any age, although it’s most common at younger ages. The most frequent location of ectopic thyroid tissue is at the base of the tongue. In 70–75% of cases is the only thyroid tissue.

The mean age of presentation is at 40.5 years. The most common symptoms are related to the growth of lingual thyroid (dysphagia, dysphonia, sleep apnea and in more severe cases respiratory obstruction and hemorrhage) and hypothyroidism, especially in the absence of orthotopic thyroid.

Case report
We present a case from a Caucasian white male, 82 years, asymptomatic, with subclinical hypothyroidism diagnosed at routine clinical evaluation. The ultrasound show a decreased size thyroid gland and head and neck CT, ordered because of other clinical problems showed a 25 mm sublingual thyroid gland, confirmed by Scintigraphy. He also did a Laringoscopy which confirmed a well defined sublingual mass. He was medicated with l-thyroxine and as he kept asymptomatic no other treatment was needed.

Conclusion
This case shows a case of a caucasian male patient with a rare congenital condition, more common in Asian women. He had a lingual ectopic gland and also a orthotopic thyroid, which only happens in 25–30% of these cases. This is probably the main reason why he kept asymptomatic most of his life, until the age of 82 (mean age of diagnosis 40.5 years) and his clinical presentation consisted only in a subclinical hypothyroidism. So, in clinical practice we should be careful precluding any condition just based on probability.

DOI: 10.1530/endoabs.32.P318

P319

Everolimus, a new therapeutic target in the metastatic neuroendocrine carcinoma
José Pérez Rodríguez1, Tomás Martín Hernández1, Cristina Hernández1, David Vicente Baz2, Virginia Martín Manzano3, Alfonso Gentil Baldrich1 & Ángel Sendón Pérez3
1Endocrinology and Nutrition Unit Clinical, Virgen Macarena University Hospital, Sevilla, Spain; 2Oncology Clinical Unit, Virgen Macarena University Hospital, Sevilla, Spain; 3Medicine School, Seville University, Seville, Spain.

Introduction
Everolimus is a drug selective inhibitor of mTOR and approved by the FDA in 2011 for treatment of neuroendocrine tumors of pancreatic origin unresectable. Our objective was to evaluate the efficacy and safety of everolimus in a patient with malignant pancreatic head insulinoma.

Case
This is a 31 year old man who complains of epigastric pain, dizziness, sweating and syncope related to exercise. During admission is objectively severe hypoglycemia (<20 mg/dl) requiring steroids and diazoxide to maintain normoglycemia. In the analyzes presented insulinemias inappropriately high (30.4–36.5 mU/ml), increased catecholamines, 5HAA and hypertransaminemia. A abdomen magnetic resonance show a lobulated injury in pancreatic head of 5 cm and multiple metastasis in liver. In a laparotomy, we observed multiple interaortocavae gastroeploic adenopathies, so we rejected the pancreatectomy. Histopathological examination revealed infiltration by neuroendocrine carcinoma type malignant insulinoma G2 (2 mI0+ca7a and Ki-67 > 7%). A Ostreoscan was negative. Chemotherapy was discarded for the low mitotic index, also the somatostatin analogs for the negativity octrescan. Finally, we decided to treat the patient with two liver chemoembolization, followed by treatment with everolimus 10 mg/24 h.

Results
During follow-up of 2 year, the tumor masses have remained similar size and radiological appearance, without evidence of new injuries. Hypertransaminemia remained stable. The patient remained euglycemic without specific treatment, even dietetic, and performs a normal life. Tolerance drug has been good without important adverse reactions.

Conclusion
Everolimus is a new treatment for pancreatic neuroendocrine tumors, especially useful in patients with great local extension or metastasis, when the surgery is not curative. Is a targeted therapy with antiproliferative effect, what slows the hormonal release, resulting in our case a control of carbohydrate metabolism. It is therefore a drug to be considered in these tumors, because good results can be obtained, as is the case in our patient.

DOI: 10.1530/endoabs.32.P319

P320

Torsade de pointes caused by gluten sensitive enteropathy leading to multiple endocrine failure; case report
Eva Csabók1, Andrea Oroz2, Péter Hankovszky1, László Rudas3 & Csaba Lengyel1
11st Department of Internal Medicine, University of Szeged, Szeged, Hungary; 2Department of Pharmacology and Pharmacotherapy, University of Szeged, Szeged, Hungary; 3Department of Anaesthesiology and Intensive Therapy, University of Szeged, Szeged, Hungary.

A 55 year-old man was brought to the emergency room because of hypotension, fatigue, fever and pain in the left shoulder. The blood glucose, sodium, potassium levels were normal. ECG showed 65/min sinus rhythm with negative T waves in the precordial leads. Blood pressure was 70/50 mmHg. Suddenly torsade des pointes occurred, which was converted to sinus rhythm with 300 mg amiodarone. Coronarography showed no significant stenosis on epicardial coronaries. During the intervention supraventricular tachycardia occurred for 30 s, and disappeared after 150 mg amiodarone, ECGs showed no PQ prolongation, 76/min sinus rhythm and diffuse T-wave depression. Echocardiography found EF 38%, anterior, inferior, septal akinesis. On the 4th and 7th day of observation 35/min bradycardia occurred with junctional and ventricular extrasystole requiring defibrillation with 200 J. TSH measurement suggested hypothyroidism (TSH: 13.89 mU/l), severe hypocalcaemia suggested hypoparathyroidism. Serum total calcium level was: 1.82 mmol/l, PTH: 1.5 pmol/l. Low serum hydrocortisone value revealed adrenal insufficiency. As the suggested diagnosis was polyglandular autoimmune syndrome we performed autoimmunne screening and found anti transglutaminase antibodies. However, further autoimmune screening showed no sign for other autoimmune diseases. Gluten-free diet, hydrocortisone, l-thyroxine, calcium, vitamin D3, and testosterone supplementation started, ICD was implanted. Torsade never occurred again. Last results showed normal Ca, TSH, IT4, IT3 values, mildly lower testosterone, suppressed ACTH and mildly elevated cortisol levels.

Conclusion
We found gluten-enteropathy caused persistent polyglandular endocrine failure leading to torsade de pointes tachycardia requiring several reanimation and ICD implantation without having autoimmune origin.

DOI: 10.1530/endoabs.32.P320

P321

Atypical parathyroid adenoma presenting with severe hypercalcemia: a case report
Husniye Baser1, Ali Karagöz2, Ferda Sevimli Burnak1, Salih Baser1, Mustafa Cayci1, Ahmet Okus3 & Meryem Ilkay Eren Karanis4
1Department of Endocrinology and Metabolism, Konya Education and Research Hospital, Konya, Turkey; 2Department of Nephrology, Konya Education and Research Hospital, Konya, Turkey; 3Department of Internal Medicine, Konya Education and Research Hospital, Konya, Turkey; 4Department of Nuclear Medicine, Konya Education and Research Hospital, Konya, Turkey.

A 55 year-old man was brought to the emergency room because of hypotension, fatigue, fever and pain in the left shoulder. The blood glucose, sodium, potassium levels were normal. ECG showed 65/min sinus rhythm with negative T waves in the precordial leads. Blood pressure was 70/50 mmHg. Suddenly torsade des pointes occurred, which was converted to sinus rhythm with 300 mg amiodarone. Coronarography showed no significant stenosis on epicardial coronaries. During the intervention supraventricular tachycardia occurred for 30 s, and disappeared after 150 mg amiodarone, ECGs showed no PQ prolongation, 76/min sinus rhythm and diffuse T-wave depression. Echocardiography found EF 38%, anterior, inferior, septal akinesis. On the 4th and 7th day of observation 35/min bradycardia occurred with junctional and ventricular extrasystole requiring defibrillation with 200 J. TSH measurement suggested hypothyroidism (TSH: 13.89 mU/l), severe hypocalcaemia suggested hypoparathyroidism. Serum total calcium level was: 1.82 mmol/l, PTH: 1.5 pmol/l. Low serum hydrocortisone value revealed adrenal insufficiency. As the suggested diagnosis was polyglandular autoimmune syndrome we performed autoimmunne screening and found anti transglutaminase antibodies. However, further autoimmune screening showed no sign for other autoimmune diseases. Gluten-free diet, hydrocortisone, l-thyroxine, calcium, vitamin D3, and testosterone supplementation started, ICD was implanted. Torsade never occurred again. Last results showed normal Ca, TSH, IT4, IT3 values, mildly lower testosterone, suppressed ACTH and mildly elevated cortisol levels.

Conclusion
We found gluten-enteropathy caused persistent polyglandular endocrine failure leading to torsade de pointes tachycardia requiring several reanimation and ICD implantation without having autoimmune origin.

DOI: 10.1530/endoabs.32.P321
Konya, Turkey; 3Department of General Surgery, Konya Education and Research Hospital, Konya, Turkey; 4Department of Pathology, Konya Education and Research Hospital, Konya, Turkey.

Introduction
Atypical parathyroid adenoma (APA) is a difficultly diagnosed tumor, including some histological features of parathyroid carcinoma (PC). In literature, no definite criteria are considered to be present to distinguish preoperatively APA from PC. It is difficult to distinguish APA and PC intraoperatively. Our report, a case applying with high levels of calcium (Ca) and intact parathyroid hormone (iPTH) and diagnosed with APA was presented.

Case
A 65-year-old woman applied to our clinic with arthralgia, myalgia and fatigue. She had severe hypercalcemia (serum Ca 17.2 mg/dl), hypophosphatemia (serum phosphate 1.9 mg/dl) in conjunction with an elevated iPTH level of 879 pg/ml. Her hemoglobin and hematocrit were elevated at 18.3 g/dl (RI: 13–17) and 52% (RI: 41–51) respectively at a recent review. He complained of lethargy and decrease in libido of 6 months duration. There was no headache or other symptoms of hyperviscosity. He is a non-smoker and there was no known pre-existing cardiopulmonary disease. He was well hydrated and there was no hepatoplenomegaly on examination. Total testosterone was noted to be elevated at 34 nmol/l (RI: 5–30 nmol/l) and FSH and LH suppressed at < 1 IU/l. He admitted to taking complementary health products to boost his virility as he had presumed that he has hypogonadism. Advice was given to stop the health products which are likely to contain testosterone. Repeated blood tests done 2 months later showed normalisation of the hemoglobin, hematocrit as well as the FSH, LH and testosterone levels without the need for testosterone therapy.

Discussion
Male hypogonadism secondary to AIDS is common and may present with non-specific symptoms. Patients may self-diagnose hypogonadism and seek unauthorised androgen therapy. We report a male patient who developed polycythemia after receiving unauthorised sources of androgen therapy.

Case report
A 42 years old man with AIDS diagnosed 10 years ago has repeatedly refused antiretroviral therapy. His most recent CD4 count was 314 cells/μl. His hemoglobin and hematocrit were elevated at 18.3 g/dl (RI: 13–17) and 52% (RI: 41–51) respectively at a recent review. He complained of lethargy and decrease in libido of 6 months duration. There was no headache or other symptoms of hyperviscosity. He is a non-smoker and there was no known pre-existing cardiopulmonary disease. He was well hydrated and there was no hepatoplenomegaly on examination. Total testosterone was noted to be elevated at 34 nmol/l (RI: 5–30 nmol/l) and FSH and LH suppressed at < 1 IU/l. He admitted to taking complementary health products to boost his virility as he had presumed that he has hypogonadism. Advice was given to stop the health products which are likely to contain testosterone. Repeated blood tests done 2 months later showed normalisation of the hemoglobin, hematocrit as well as the FSH, LH and testosterone levels without the need for testosterone therapy.

Conclusion
Male hypogonadism secondary to AIDS can result from testicular infiltration by opportunistic infections, medications suppressing the hypothalamic–pituitary–gonadal axis or be associated with advanced immunosuppression. It is important to routinely screen for symptoms of hypogonadism and if the diagnosis confirmed biochemically, to start testosterone replacement therapy with close monitoring of the hematocrit. Clinicians must be cognisant of possible androgen abuse. Self-initiation of androgen therapy with no monitoring can result in polycythemia and dire consequences.

DOI: 10.1530/endoabs.32.P323

P322
Severe hyponatraemia in patients admitted to acute medical unit
Mitra Sadeghi, Abu Ahmed & Sanjaya Dissanayake
Blackpool Teaching Hospitals, Blackpool, UK.

In a retrospective cohort study, we reviewed the medical notes of patients with severe hyponatraemia admitted to acute medical unit at Blackpool Hospital between January and March 2012. We assessed the severity, causes of hyponatraemia, length of stay and mortality in patients with hyponatraemia. We identified 25 patients with plasma sodium ≤ 120 mmol/l, 5 of whom were admitted twice during the study period. Their average age was 70 (range 30–91) years, 16 were female and 9 were males. Three of them with sodium admitted twice during the study period. Their average age was 70 (range 30–91) years.

Reasons for admission include confusion in 24% of patients, collapse in 20%, falls in 20%, and vomiting 8%. Elven patients (44%) were found to have hypovolaemic hyponatraemia, nine patient had hyperosmolar hyponatraemia related to heart and liver diseases, and five patients had normovolaemic hyponatraemia related to SIADH related to drug therapy. Hyponatraemia was corrected within a week in eight patients (32%), and was corrected between 1 and 4 weeks in seven patients (28%), and never corrected in seven patients.

Length of hospital stay was more than a week in 13 patients (56%), and 44% of patients stayed for more than a week. Mortality was 16%.

Severe hyponatraemia in acute medical admission is associated with prolonged hospital stay, and high mortality.

DOI: 10.1530/endoabs.32.P322

P323
Androgen abuse complicated by polycythemia in a man with acquired immunodeficiency syndrome (AIDS)
Cheng Jye Seow, Wei Liang Abel Chen, Shang Ming Samuel Lee, Liu Yuan Gabriel Cher & Wei Feng Lee
Tan Tock Seng Hospital, Singapore, Singapore.

Introduction
Male hypogonadism secondary to AIDS is common and may present with non-specific symptoms. Patients may self-diagnose hypogonadism and seek unauthorised androgen therapy. We report a male patient who developed polycythemia after receiving unauthorised sources of androgen therapy.

Case report
A 42 years old man with AIDS diagnosed 10 years ago has repeatedly refused antiretroviral therapy. His most recent CD4 count was 314 cells/μl. His hemoglobin and hematocrit were elevated at 18.3 g/dl (RI: 13–17) and 52% (RI: 41–51) respectively at a recent review. He complained of lethargy and decrease in libido of 6 months duration. There was no headache or other symptoms of hyperviscosity. He is a non-smoker and there was no known pre-existing cardiopulmonary disease. He was well hydrated and there was no hepatoplenomegaly on examination. Total testosterone was noted to be elevated at 34 nmol/l (RI: 5–30 nmol/l) and FSH and LH suppressed at < 1 IU/l. He admitted to taking complementary health products to boost his virility as he had presumed that he has hypogonadism. Advice was given to stop the health products which are likely to contain testosterone. Repeated blood tests done 2 months later showed normalisation of the hemoglobin, hematocrit as well as the FSH, LH and testosterone levels without the need for testosterone therapy.

Discussion
Male hypogonadism secondary to AIDS can result from testicular infiltration by opportunistic infections, medications suppressing the hypothalamic–pituitary–gonadal axis or be associated with advanced immunosuppression. It is important to routinely screen for symptoms of hypogonadism and if the diagnosis confirmed biochemically, to start testosterone replacement therapy with close monitoring of the hematocrit. Clinicians must be cognisant of possible androgen abuse. Self-initiation of androgen therapy with no monitoring can result in polycythemia and dire consequences.

DOI: 10.1530/endoabs.32.P323

P324
Abstract withdrawn.

DOI: 10.1530/endoabs.32.P324

P325
A rare presentation of DRESS-associated thyrotoxicosis and myocarditis: case report
Wei Feng Lee, Cheng Jye Seow & Michelle Jong
Tan Tock Seng Hospital, Singapore, Singapore.

Introduction
Drug rash with eosinophilia and systemic symptoms (DRESS) is a severe drug eruption with systemic involvement. Visceral manifestations consisting of fulminating hepatic failure, myocarditis, interstitial nephritis, pneumonitis and autoimmune hypothyroidism are known sequelae. We report a case of DRESS syndrome post Bactrim (sulfamethoxazole and trimethoprim) therapy complicated by both myocarditis and autoimmune thyrotoxicosis.

Case report
A previously well 18 years old gentleman was prescribed Bactrim for acne vulgaris and developed DRESS syndrome 2 weeks later. He was started on high dose steroids. 2 months into steroid therapy, he presented at the Emergency Department for fever and decreased effort tolerance. He was critically ill with tachycardia (Heart Rate 150 bpm), hypotension (Blood Pressure 70/40 mmHg)
and an ejection fraction of 20% on 2D-echocardiography. There were multiple episodes of unstable ventricular tachyarrhythmias requiring cardioversion and intubation. Thyroid panel revealed free T4 5.60 (RI 3.5–6.0), TSH 0.04 (RI 0.0–6.0 U/ml) and free T3 6.4 (RI 3.5–6.0). Thyroid autoimmune markers were positive (TPO Ab 68.8 (RI 0–60 U/ml), TRAB 14.8 (RI 0–1.5 IU/l). He was treated for possible thyroid storm with propylthiouracil and hydrocortisone. He also had severe myocarditis with hypotension refractory to inotropic support and intra-arterial balloon pump. Extracorporeal membrane oxygenation (ECMO) was initiated but patient continued to deteriorate and unfortunately passed away 5 days after admission.

Conclusion
Despite high dose immunosuppression and cessation of the causative agent post DRESS, multiple autoimmune sequelae may develop and may unfortunately be life threatening. Both patients and clinicians need to be cognisant of this. Early diagnosis and treatment may potentially be life saving.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research project.

Funding
This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

DOI: 10.1530/endoabs.32.P325

### P326

**Radiation-induced primary hypothyroidism in patients with head and neck cancer**

Raluca Tifanescu1,2*, Oana Ion1, Mara Carsote1 & Catalina Poiana1,2

1 Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; 2 C. I. Parhon National Institute of Endocrinology, Bucharest, Romania; 3 Al. Trestioreanu Institute of Oncology, Bucharest, Romania.

**Background**

Hypothyroidism is a frequent side effect of external radiotherapy of the cervical region for head and neck cancer. Up to 33% of irradiated patients developed primary hypothyroidism within 2 years after radiation therapy. The risk of hypothyroidism increases with radiation dose.

**Patients and methods**

Four patients (2M/2F), aged 53.3 ± 13.9 years, were diagnosed with hypothyroidism after cervical irradiation for head and neck cancer. TSH and FT4 were measured by chemiluminescence.

**Case reports**

Patients received external-beam radiation therapy delivered in the form of photon beams, for undifferentiated cervix carcinoma, oropharyngeal cancer, epidermoid spinocellular carcinoma of palate tonsil and laryngeal carcinoma; median radiation dose was 63 Gy. Median time from radiotherapy to diagnosis of hypothyroidism was 3.5 years (range: 0.5–9 years). Median TSH at diagnosis was 55 mIU/l (range: 5.97–100 mIU/l). TPO antibodies and antithyroglobulin antibodies were negative in all patients. All patients but one presented marked thyroid atrophy. Hypothyroidism was complicated with pericarditis in two patients.

**Conclusion**

Thyroid screening is mandatory for an early diagnosis of radiation-induced primary hypothyroidism and for prevention of hypothyroidism complications.

DOI: 10.1530/endoabs.32.P326

### P327

**A case of type 1 diabetes represented by diabetic ketoacidosis after isotretinoin therapy: is it a result or coincidence?**

Selcuk Burak Polat, Muhammed Sacikara, Berna Evranos, Caffer Kay, Reyhan Ersoy & Bekir Cakir

Endocrinology Department, Ataturk Research Hospital, Yildirim Beyazit University, Ankara, Turkey.

**Well-known environmental factors which can lead to type 1 diabetes are viral infections, vaccines, diet, exposure to cow milk in infancy, vitamin D deficiency, drugs, maternal age, preeclampsia and low birth weight. Isotretinoin is an effective drug for acne treatment. It can cause dyslipidemia, elevated liver enzymes, insulin resistance and type 2 diabetes. Our case is type 1 diabetes developed after the use of isotretinoin and represented with diabetic ketoacidosis.**

18-years-old male patient has admitted to hospital with complaints of abdominal pain, increased sense of thirst, frequent urination and dry mouth. In physical examination, he was dehydrated with hypotension and dry oral mucosa. He did not have family history of diabetes. With further questioning, we have learnt that he was using isotretinoin for acne treatment for 7 months. In laboratory examination, his plasma glucose level was 400 mg/dl, had heavy ketonuria and acidosis in arterial blood gas. He was hospitalized in endocrinology ward with diagnosis of diabetic ketoacidosis. Hydration with isotonic saline together with intensive insulin therapy and blood glucose levels were regulated.

**Conclusion**

Isotretinoin is related with metabolic syndrome and type 2 diabetes because of worsened insulin resistance. However, there are few cases of type 1 diabetes in literature. Anti GAD positivity is suggestive of underlying autoimmune mechanisms triggered by the drug. Patients should be monitored with frequent plasma glucose levels during treatment.

DOI: 10.1530/endoabs.32.P327

### P328

**Lithium-associated hyperparathyroidism: a case report**

Yuksel Altuntas1, Fezya Yener Ozturk2 & M. Serdar Yildiz2

1 Department of Endocrinology and Metabolism, Sisli Etfal Training and Research Hospital, Istanbul, Turkey; 2 Department of Internal Medicine, Sisli Etfal Training and Research Hospital, Istanbul, Turkey.

**Introduction**

Lithium carbonate therapy has continued to be a mainstay treatment for bipolar disease and schizophrenia. Hypercalcemia and hyperparathyroidism (HPT) is an underappreciated, but relatively common occurrence, with a prevalence ranging from 6.3 to 50% in patients requiring long-term lithium therapy. It is still unclear whether lithium initiates HPT or promotes an underlying subclinical state. Lithium antagonizes the calcium-sensing receptor (CASR) resulting in an increase in the threshold level of calcium required for suppression of serum PTH. This is validated by the fact that many patients with lithium associated hyperparathyroidism (LAH) have inappropriately low-normal urinary calcium excretion. LAH reflects a spectrum of disease from single to multigland involvement with a variable response of each parathyroid gland to the continuous PTH stimulation.

**Case report**

A 52-year-old female with bipolar disorder who had been treated with 900 mg lithium per day for 2 years, was referred to our endocrine out-patient clinic for evaluation of hypercalcemia. She denied having any symptoms related to hypercalcemia. Her blood and urine tests were as follows: serum calcium: 10.9 mg/dl (normal range: 8.6–10.2 mg/dl), phosphorus: 3.4 mg/dl (normal range: 2.6–4.3), creatinine: 0.8 mg/dl (normal range: 0.95), PTH: 191 pg/ml (normal range: 15–65), 24-h urinary calcium: 66 mg/day (normal range: 100–321). Her bone mineral densitometry showed reduced T-score: −2 (neck of femur), −1, 3(spine). Parathyroid scintigraphy with Tc-99m MIBI showed a parathyroid pathology with an isotope retention at lower pole of left thyroid gland. She was diagnosed as LAH. After consultation with her psychiatrist, lithium therapy was stopped. As she did not meet the criteria for parathyroid surgery of asymptomatic hyperparathyroidism, a conservative approach to therapy was thought to be appropriate. After 2 weeks of cessation of lithium therapy, her serum calcium decreased to 10.1 mg/dl.

**Conclusion**

Approximately 10–15% of lithium treated patients become hypercalcemic with findings suggestive of HPT. By routinely monitoring serum calcium levels and long-term follow-up, healthcare providers can reduce the morbidity and improve the quality of life.

DOI: 10.1530/endoabs.32.P328

### P329

**Thyrotoxic periodic paralysis in young Caucasian**

Nikola Simovic, Zoran Gluvic, Zorica Rasic-Milutinovic, Jelena Tica, Vesna Popovic-Radinovic, Marina Vujovic & Milena Lackovic

School of Medicine, Zemun Clinical Hospital, Belgrade, Serbia.

**Thyrotoxic periodic paralysis (TPP) is uncommon complication of Graves’ disease mainly observed in young males of Asian origin. It is rarely seen among**

Endocrine Abstracts (2013) Vol 32
white hyperthyroid patients (0.1–0.2%), usually presented as lower extremities muscle weakness of sudden onset, probably cause by hypokalemia. Possible mechanism of hypokalemia is an increased sodium-potassium-adenosine triphosphatase pump activity with consequent massive shift of potassium from extracellular to the intracellular compartment, with no change in the total body potassium levels.

We presented a 53-year-old Caucasian male with significantly increased levels of free thyroxine associated with newly diagnosed diffuse toxic goitre. Unexpectedly, the patient experienced sudden muscle weakness with immobility at the second hospital day. Because of suspicion that this condition was an adverse effect of propylthiouracil (PTU), drug was immediately stopped. Repeated biochemistry findings revealed extremely low levels of serum potassium and elevated extracellular to the intracellular compartment, with no change in the total body potassium levels. Control biochemistry showed normal potassium levels. Further thyro sup-presitive treatment was continued with methimazole and propranolol, gradual restoration of muscle strength and full mobility was achieved within few hours. Control biochemistry showed normal potassium levels. The ultrasound structure of thyroid was heterogeneous. However, polyarthritids symptoms were quite severe, with the presence of rheumatoid factor. The patient also had no complaints of symptoms of vaginismus, which confirmed her husband. Propylthiouracil withdrawal was not enough for the resolution of symptoms. After administration of 40 mg of prednisone and 5 mg bisoprolol, joint symptoms subsided and we observed clinical celsiusythes. Further treatment follow in the country of residence of our patients. Thyroidectomy was performed successfully, and the patient’s condition, according to her family remained good. Unfortunately, we know nothing about the further course of vaginismus.

Discussion

Short treatment time did not allow us more detailed diagnosis of the causes and possible treatment of vaginismus. It is difficult to clearly identify the possible pathological mechanism linking disorders seen in our patient. Because of mild hyperthyroidism, hormonal disturbance are unlikely as a cause of vaginismus. More likely, it seems already described in Sjogren’s syndrome, is autoimmune mechanism. However, this remains speculation.

DOI: 10.1530/endoabs.32.P331

P330 Persimmonious indications for thyroideectomy in chronic thyroiditis

Mihai Radu Diaconescu, Mihai Gîlî, Ioan Costea, Mirela Grigorovici & Smaranda Diaconescu
1 Gr T Popa’ University of Medicine and Pharmacy, I V th Surgical Clinic, Iasi, Romania; 2 Gr T Popa’ University of Medicine and Pharmacy, I V th Pediatric Clinic, Iasi, Romania.

Background

Chronic inflammatory processes of the thyroid represents an important proportion of the gland’s pathology but the majority of them must be treated by nonsurgical methods, thyroidectomy remaining circumstantially indicated.

Patients and methods

In 14 cases (3%) from 464 operations for different thyroid lesions we have encountered authentic inflammatory processes in nine cases of Hashimoto’s thyroiditis, associated with papillary thyroid carcinoma and one with malignant lymphoma, two cases of Riedel’s thyroiditis and de Quervain’s thyroiditis, tuberculous thyroiditis and thyroid actinomycosis one case each respectively. The clinical and imaging data, biological evaluation and titer of the antibodies but the intraoperative estimations together with the paraffine examination were determinative for the diagnosis.

Results and discussions

Firm diagnosis of thyroiditis was rarely affirmed before the operation, indication for surgery being formulated on clinical criterions dominated by the cancer suspicion. Among them the diffuse or (multinodular thymegaly with a dominant nodule with recent apparition and accelerate growing, hard consistence, compressive or celsian features and adenopathy in temporal or geographic proximity of the Cemobyl disaster. More added the imaging tests but especially the suspect aspects of the FNAB (follicular smears or with Hurthle cells) and also of the frozen sections. Certainty diagnosis was established by the paraffin examination not always without histations or re-examinations (In one case of Hashimoto’s thyroiditis the final diagnosis was a malignant lymphoma). A large near total removal of the thyroid gland decided after Intraoperative findings induced for the most of our patients an obvious tendency toward hypothyroidism which must be monitorised and corrected for prolonged periods.

Conclusions

All the diagnosis resources must be exhausted for the precise diagnosis of the inflammatory lesions of the thyroid to avoid the unnecessary surgery. On the other side, the overstimulation by the TSH of the thyroid tissue affected by the inflammatory process represent an important neoplasia producing stimulus.

DOI: 10.1530/endoabs.32.P330

P331 The coexistence of vaginismus with arthritis after pharmacological treatment of hyperthyroidism: is it only a coincidence?

Krzysztof Marczewski1,2 & Marek Maciejewski 1

1John Paul II Regional Hospital, Zamosc, Poland; 2Zamosc University of Management and Administration, Zamosc, Poland.

Introduction

Both thyroid dysfunction and sexual dysfunction in young women are relatively common. Even is described the correlations between various types of sexual dysfunction in women, and the severity of hyperthyroidism. However, it is known to us a description of the coexistance of vaginismus with arthritis, a relatively rare complication of antihyroid treatment.

Case report

25-year-old woman was admitted to hospital with symptoms of polyarthritids which occurred during treatment of hyperthyroidism propylthiouracil. Methimzo-lol previously used, was discontinued due to skin allergy. Clinical and biochemical signs of hyperthyroidism were relatively mild (TSH = 0.13 mU/l; FT3 4.8 pg/dl; FT4 1.65 ng/dl) with slightly elevated antithyroid autoantibody. The ultrasound structure of thyroid was heterogeneous. However, polyarthritids symptoms were quite severe, with the presence of rheumatoid factor. The patient also had no complaints of symptoms of vaginismus, which confirmed her husband. Propylthiouracil withdrawal was not enough for the resolution of symptoms. After administration of 40 mg of prednisone and 5 mg bisoprolol, joint symptoms subsided and we observed clinical celsiusythes. Further treatment follow in the country of residence of our patients. Thyroidectomy was performed successfully, and the patient’s condition, according to her family remained good. Unfortunately, we know nothing about the further course of vaginismus.

Discussion

Short treatment time did not allow us more detailed diagnosis of the causes and possible treatment of vaginismus. It is difficult to clearly identify the possible pathological mechanism linking disorders seen in our patient. Because of mild hyperthyroidism, hormonal disturbance are unlikely as a cause of vaginismus. More likely, it seems already described in Sjogren’s syndrome, is autoimmune mechanism. However, this remains speculation.

DOI: 10.1530/endoabs.32.P331

P332 Crystal structure of the complex between an insulin-like peptide (DILP5) and an ILP binding protein (IMP-L2) from Drosophila melanogaster

Nikolaj Kulahitin1, Christopher J Watson1, Waseem Sajjad1, Gerd Schluckebier2, Asser S Andersen2, Andrzej M Brzozowski3 & Pierre De Meyts1
1Novo Nordisk A/S, Gentofte, Denmark; 2Novo Nordisk A/S, Ma˚løv, Denmark; 3University of York, York, UK.

The insulin signalling system including the insulin receptor tyrosine kinase (IRTK) is evolutionarily ancient and appears in the first multicellular organisms (Chordarians). The Drosophila melanogaster genome contains seven genes for insulin-like peptides (ILPs) that are expressed in neurosecretory cells in a highly tissue- and stage-specific pattern, DILP1-7. There is however only one IRTK (dIR). This system is important in the regulation of metabolism, growth, reproduction and lifespan.

We reported in 2011 the crystal structure of Drosophila insulin-like peptide 5 (DILP5) (expressed in Saccharomyces cerevisiae) at 1.85A resolution, as well as its biological and receptor binding properties. DILP5 shares the canonical fold of the insulin peptide family and form dimers that differ from the mammalian and hagfish insulin dimers.

Drosophila melanogaster also has a circulating ILP binding protein, called imaginal morphogenesis protein-Late 2 (IMP-L2), with no equivalent in mammals. It was cloned, expressed and purified in 2000 and was shown to bind human insulin and insulin-like growth factors. We showed in 2011 that it also binds DILPS. The knockout of IMP-L2 is embryonic lethal. We now report the solution of the crystal structure of IMP-L2 in the free form as well as bound to DILPS. Recombinant IMP-L2 was expressed in a Baculovirus expression system, purified and crystallized with selenium as heavy atom.

IMP-L2 showed as predicted from the sequence a bilobed structure with two IgG antibody, with slightly elevated antithyroid autoantibody. The ultrasound structure of thyroid was heterogeneous. However, polyarthritids symptoms were quite severe, with the presence of rheumatoid factor. The patient also had no complaints of symptoms of vaginismus, which confirmed her husband. Propylthiouracil withdrawal was not enough for the resolution of symptoms. After administration of 40 mg of prednisone and 5 mg bisoprolol, joint symptoms subsided and we observed clinical celsiusythes. Further treatment follow in the country of residence of our patients. Thyroidectomy was performed successfully, and the patient’s condition, according to her family remained good. Unfortunately, we know nothing about the further course of vaginismus.

Discussion

Short treatment time did not allow us more detailed diagnosis of the causes and possible treatment of vaginismus. It is difficult to clearly identify the possible pathological mechanism linking disorders seen in our patient. Because of mild hyperthyroidism, hormonal disturbance are unlikely as a cause of vaginismus. More likely, it seems already described in Sjogren’s syndrome, is autoimmune mechanism. However, this remains speculation.

DOI: 10.1530/endoabs.32.P331
The complex of IMPL-2 with DILP5 showed a multimeric structure with two DILP5 molecules bound into the grooves between the beta sheets of two distinct IMPL-2s in a symmetrical tetrameric IMPL-2. The structural differences between the free and bound forms will be discussed.

DOI: 10.1530/endoabs.32.P332

**P333**

Changes in sexual orientation in gender identity disorder: evaluation of their association to sex reassignment surgery and cross-sex hormone treatment

Matthias Auer1,2, Johannes Fuss2, Anastasia Athanasouli1, Guenter Stalla1 & Caroline Sievers1

1Max Planck Institute of Psychiatry, Munich, Germany; 2Central Institute of Mental Health, Mannheim, Germany.

Objective

Sexual orientation in males and females is considered to be determined in early life and to be virtually unchangeable in the course of adulthood. In contrast some transsexuals report a change in their sexual orientation most often following sex reassignment procedures. The reason for this phenomenon is unknown.

Methods

We asked 106 transsexual (66 MtF and 40 FtM) patients from our endocrine outpatient clinic to complete a questionnaire, retrospectively evaluating the history of their gender transition phase. A special focus was sexual orientation and prevalence and recalled time point of changes in their sexual orientation.

Results

FtM were most frequently heterosexual, according to their gender identity, while MtF more often reported to be homosexual (72.5 vs 29% and 33.8 vs 7.5% respectively; P<0.001). MtF reported change in sexual orientation in total in 32.8% of cases in contrast to FtM with only 17.5% (P=0.067). 6 MtF (21.4%) reported change in sexual orientation without any sex reassignment surgery in their history in contrast to only 2 FtM (12.5%). Of those who had undergone sex reassignment surgery, most but not all subjects had experienced changes in their sexual orientation following the surgical procedure (13 MtF (73.5%), 5 FtM (71%)). While there was no significant difference seen in terms of time interval between date of introduction of cross-sex hormone treatment and changes in sexual orientation following the surgical procedure (13.8 vs 1.75 years P<0.05). In contrast to earlier reports, we showed that changes in sexual orientation do not solely occur in the context of sex reassignment surgery. Furthermore, there are clear differences between MtF and FtM, who especially reported a significantly longer interval from sex reassignment surgery to the change in sexual orientation.

Conclusion

P335

The distinctive roles of thyroid hormone receptors in the development of zebrafish tissues

Federica Marelli1 & Luca Persani1,2

1IRCCS Istituto Auxologico Italiano, Milan, Italy; 2University of Milan, Milan, Italy.

Introduction

As in humans, thyroid hormone (TH) plays an essential role on zebrafish development by acting through the specific nuclear receptors (TRα or TRβ) and activating/suppressing the expression of several target genes. In zebrafish, TRs is preferentially expressed in the heart and CNS while the TRβ is mainly expressed in the retina and inner ear, but the specific role of these receptors in the different target tissues is presently unknown. In this study, we tested the role of TH and TRs during Zebrafish development and a particular attention has been devoted to the examination of the following target tissues brain, heart, sensory organs (retina and otoliths).

Methodology

Somatic and transgenic zebrafish lines are injected with morpholinos, to knockdown the expression of the TRs and producing two different defective lines, MOs_TRα and MOs_TRβ. The morphological and functional anomalies of MOs_TRs were compared with MOs_ctrl at several time-points using different techniques: whole mount in situ hybridization, immunohistochemistry, histologic sections and confocal microscopy.

Results

Both defective morphant-fish lines display a series of growth alterations that depend on the type of defective-receptor and the preferential expression of the TR at tissue-level. i) Brain development: MOs_TRα show a severe cerebral hypoplasia and edema that impairs the proper CNS formation, while MOs_TRβ are quite comparable with controls. ii) Cardiac function: both MOs lines show structural and functional alterations compared to MOs_ctrl. MOs_TRβ heart is heavily hypotrophic and bradycardic whilst MOs_TRβ are hypertrophic and tachycardic. iii) Sensory organs: only MOs_TRβ display severe abnormalities both in photoreceptors and otoliths (corresponding to the mammal inner ear) formation.

Discussion

Zebrafish is an excellent model to study the role of THs and TRs during embryonic development, representing an interesting and new biotool to test human TRα and TRβ mutations.

DOI: 10.1530/endoabs.32.P335

**P334**

Somatostatin receptor sst2 transfer in somatolactotroph cell line. Constitutive activity and drug sensitivity

Catherine Roche1,2, Thomas Graillon1,2, Ramaherizo Rasolofanjahary1, Sylvie Thirion1, Alain Enjalbert1,2, Corinne Gerard1 & Anne Barlier1,2

1Research Center of a Neurophysiology of Marseille, UMR7286-CNRS, Aix-Marseille University, Marseille, France; 2Laboratory of Molecular Biology, Centre Hospitalo Universitaire Conception, Marseille, France; 3Department of Neurosurgery, Centre Hospitalo Universitaire Timone, Marseille, France.

Somatostatin is a ubiquituous neuropeptidic inhibitor of various cellular functions including endocrine and exocrine secretion. Moreover, this peptide may control cell proliferation in normal and tumoral tissues. Somatostatin biological effects are mediated by five subtype of G protein-coupled receptor, sst1 through sst5. The somatostatin analogs have high affinity for sst2 receptor and the success of in vivo peptide therapy is correlated with high levels of sst2 in the adenomas.

We previously demonstrated the re-sensitivity of human somatotroph adenomas to a somatostatin analog (octreotide) by sst2 expression after adenoviral transfer in adenomas cells in vitro. A ligand-independent activity of sst2 was also demonstrated in human adenomas in this study through an increase in the mortality and a decrease in secretion. Several GPCRs have been shown to exhibit varying degrees in ligand-independent activity including sst2 in a pancreatic adenocarcinoma models and in a corticotroph context.

To investigate more specifically the sst2 ligand-independent and ligand-dependant activity and their impact on cell physiology as proliferation and secretion in somatolactotroph context, an sst2 expressing cell line was generated after lentiviral transfer in the rat somatolactotroph cell line (GH4C1) and compared in vivo and in vitro to a eGFP-GH4C1 cell line. Sst2 mRNA level, sst2 immunostaining and somatostatin binding sites demonstrated a strong sst2 expression in this cell line. The level of somatostatin binding was closer to that found in human somatotroph adenomas.

A ligand independent impact of sst2 was observed on cAMP level, ERK activity, hormonal secretion and, to a lesser extent, on cell viability in early proliferation step, in vitro and in vivo. Moreover, the octreotide sensitivity was consistently improved in vitro and in vivo, after sst2 transfer.

In conclusion, we have validated a somatotroph cell line, a useful tool to evaluate DILP5 molecules bound into the grooves between the beta sheets of two distinct IMPL-2s in a symmetrical tetrameric IMPL-2. The structural differences between the free and bound forms will be discussed.

DOI: 10.1530/endoabs.32.P334
P336
Effects of pharmacological and genetic manipulation of glucocorticoids during early development of the zebrafish embryo
Kathryn Wilson, Gianfranco Matrone, Carl Tucker, Patrick Hadoke, Christopher Kenyon, John Mullins & Martin Denvir
University of Edinburgh, Edinburgh, UK.

Background
The effects of glucocorticoids (GC) on the developing zebrafish embryo (Zfe) are poorly characterised. We have assessed the effects of pharmacological and genetic manipulation of cortisol and glucocorticoid receptors (GR) on global development and stress response during the first 120 hpf.

Methods
Cortisol production was modulated by inhibiting the enzyme 11b hydroxylase using morpholino gene knockdown (MO) or incubation in the drug metyrapone (MeT) (10 μM). Downstream effects of GC were modulated using the GR agonist dexamethasone (Dex), GR antagonist RU486 or GR knockdown using targeted MO (GR-MO). The effects of these modulations on global development (head–trunk angle, growth-rate and swim bladder inflation), hatch-rate, whole embryo cortisol (WEC) levels, stress response (to stirring) and spontaneous swim behaviour were assessed.

Results
Global development was delayed by approximately 8 h following inhibition of GR mediated effects (Ru486 and GR-MO) but accelerated by Dex. This alteration was more apparent in the first 72 hpf with catch-up in growth by 96 hpf. Spontaneous hatching from the chorion was also delayed by inhibition of GR and accelerated by Dex. Inhibition of GR also resulted in altered swim behaviour. Cortisol levels (WEC) increased following stress in control embryos at 72 hpf but not at earlier stages 36 hpf (6.7 ± 0.008 ng/embryo compared to 0.709 ± 0.16 ng/embryo respectively). This rise in WEC could be abolished with Met and MO treatment at 72 hpf but was unaffected at 36 hpf suggesting inactivity of this pathway at earlier developmental stages. Met and MO treated Zfe displayed abnormal post stress swim patterns, with reduced motility following stress compared to controls.

Conclusions
Stress response appears to be established in the Zfe by 72 hpf and can be modified by pharmacological and genetic manipulation of GC pathways without impairing global development significantly. These modifications result in altered hatching rates and swim behaviour.

DOI: 10.1530/endoabs.32.P336

P337
A study on the relationship between energy reserves and energy expenditure during the time of male puberty
Afzaal Ahmed Naseem1, Nadia Afza1, Ayessa Younus1, Muhammad Saqlain2, Midhat Fatima1, Shaista Aslam1, Muzhar Qayyum1 & S S R Rizvi1,3
1Department of Zoology, PMAS Arid Agriculture University, Rawalpindi, Pakistan; 2Department of Zoology, Government College University, Lahore, Pakistan; 3Pakistan Science Foundation, Islamabad, Pakistan.

Leptin, a key metabolic signal controlling both energy intake and energy reserves, informs the brain about energy stores of the body to initiate reproductive processes at puberty. Thyroid hormones are important determinant of overall energy expenditure, basal metabolic rate and thermogenesis. The present study examined the relationship between leptin and thyroid hormone (T₃) and triiodothyronine (T₄) in boys (n = 540) between the age of 1 and 20 years. Blood samples were collected and plasma concentrations of leptin, T₃ and T₄ were measured using specific ELISA. Data were analyzed using Student’s t-test, ANOVA and Pearson correlation r. Concentrations of leptin increased from 8th year, peaked at 10th year and gradually declined to lowest concentrations at 18th year. Concentrations of T₄ were higher at 1st year, increased to highest concentrations at 2nd, declined to lowest level at 4th and rose to peak at 5th year. T₃ concentrations declined from 9th year to lower levels between 11th and 13th year, rose to peak at 15th year and declined to lower levels between 16 and 20 years. T₄ concentrations exhibited a plateau from 1 to 3rd year, declined to lowest levels at 4th year and gradually increased at 6th year to be maintained by 8th year. T₃ concentrations rose at 9th year, progressively increased to peak at 17 years, slightly declined at 18 years to be maintained by 20th year. Leptin and T₄ concentrations were positively correlated at infancy and puberty, negatively correlated at early puberty and positively correlated at mid and late puberty/adolescence. Leptin and T₃ concentrations were positively correlated at infancy, negatively correlated at prepuberty, positively correlated at early puberty and negatively correlated at mid and late puberty/adolescence. In conclusion, concentrations of leptin, an indicator of energy reserves, are negatively correlated with T₄, a marker of energy expenditure at mid and late puberty/adolescence.

DOI: 10.1530/endoabs.32.P338

P338
TurboFlow-LC-MS/MS method for quantification of DHEA, DHEAS, 17α-hydroxyprogesterone, Δ4-androstenedione and testosterone in children
Tae Snejberg, Hanne Frederiksen, Trine Holm Johanssen, Anders Juul & Anna-Maria Andersson
Department of Growth and Reproduction, Rigshospitalet, Faculty of Health and Medical Sciences, Copenhagen University Hospital, University of Copenhagen, Copenhagen, Denmark.

Diagnosis and management of infants and children with sex steroid disorders requires fast and simultaneous assessment of several sex steroid metabolites in serum at low concentrations and on small sample volumes. Therefore, we developed a sensitive and selective TurboFlow-LC-MS/MS method for quantification of DHEA, DHEAS, 17α-hydroxyprogesterone, Δ4-androstenedione and testosterone in serum from pre-pubertal children.

Total run time was 10.75 min with the effluent being directed to the mass spectrometer for 2.6 min. Limits of quantification were determined as described by the International Conference on Harmonisation (ICH) with the following values: DHEA, 0.88 nM; DHEAS, 48 nM; 17α-hydroxyprogesterone, 0.19 nM; Δ4-androstenedione, 0.18 nM and testosterone, 0.10 nM. Intra-day relative S.D. ranged from 4.6 to 13.8% and inter-day relative S.D. ranged from 5.7 to 15.7%. Steroid concentrations in 186 serum samples from children (8.4–14.8 years old) were compared with results obtained by immunoassays for DHEAS, Δ4-androstenedione and testosterone. DHEAS and testosterone gave overall similar results with mean values 19 and 18% higher, respectively by LC-MS/MS, while levels of Δ4-androstenedione on average were found to be 83% higher when analysed by immunoassay. DHEA was quantified in all samples with both methods, while Δ4-androstenedione and testosterone were quantified in 78 and 61% of the samples, respectively using immunoassay and in 98 and 94% of the samples, respectively using the LC-MS/MS method. Concentrations of the five steroids determined by LC-MS/MS were similar to previously published results. The presented method is suitable in a clinical setting for simultaneous quantification of five steroids important for management of children with disorders of sex development and steroid biosynthesis defects. Our study illustrates the importance of LC-MS/MS technology for quantification of – at least – Δ4-androstenedione and testosterone at low levels in children as an alternative to conventional immunoassays.

DOI: 10.1530/endoabs.32.P339

P339
The prevalence, incidence and diagnostic delay in 46,XY females; a Danish national cohort study
Agnethe Berglund1, Kirstine Stockholm1, Jens Fedder2 & Claus Højbjerg Gravholt1,3
1Department of Endocrinology and Internal Medicine, Århus University Hospital, Nørrebrogade 44, Århus, Denmark; 2Fertility Clinic, Odense University Hospital, Odense, Denmark; 3Department of Molecular Medicine, Århus University Hospital, Århus, Denmark.

Introduction
Disorders of sex development where females have a 46,XY karyotype can be seen. Main reasons for this are the conditions of androgen insensitivity syndrome (AIS) and gonadal dysgenesis. The clinical phenotype of both conditions is variable and can present from an undervirilized or infertile male to an individual with ambiguous genitalia who first present in adolescence with primary amenorrhoea and/or delayed puberty. The aim of the study was to estimate prevalence, incidence and diagnostic delay in 46,XY females in an unselected population in a nationwide study.

Design
A retrospective cohort study.

Patients and methods
From the Danish Cytogenetic Registry data of all cases registered as females and diagnosed with 46,XY or a related male karyotype in Denmark during 1965–2010 were retrieved. Cases were divided into subgroups of females having a 46,XY karyotype, mosaicism (45,XX/46,XY) and ‘other karyotypes’.
Endocrine Abstracts (2013) Vol 32

Information of the background population was retrieved from Statistics Denmark. Results
Age at diagnosis was mainly distributed in two periods with 29% diagnosed within the first year of life and 38% diagnosed during adolescence (13–20 years). Median age at diagnosis was 11.6 years (range: 0–46 years) and age at diagnosis increased significantly during the study period (P = 0.005). There was no difference in age at diagnosis comparing the subgroups (Kruskal–Wallis Rank Sum = 642). A prevalence of approximately six cases per 100 000 was observed during 1996–2010. During 1971–1990, the highest prevalence was observed with 13 cases per 100 000. From 1996 and forward the prevalence decreased.

Conclusions
Females with 46,XY and related male karyotypes are diagnosed with considerable diagnostic delay. Time trend in age at diagnosis shows increasing age at diagnosis during the study period. The prevalence of 46,XY female is higher than previously reported.

DOI: 10.1530/endoabs.32.P339

P340
Effects of prenatal antiandrogen exposure on HSD3B expression in the fetal porcine gonads
Katarzyna Knapczyk-Stwora & Malgorzata Grzesiak
Department of Endocrinology, Institute of Zoology, Jagiellonian University, Krakow, Poland.

3β-hydroxysteroid dehydrogenase/Δ5,Δ4-isomerase (HSD3B) is a key enzyme catalyzing an essential step in the formation of all classes of steroid hormones. Previously, we have reported the presence of androgen receptors in the fetal porcine gonads denoting the role of androgens during gonadal development. There is also growing evidence that steroid hormones modulate HSD3B expression. Thus, the aim of the present study was to determine the effect of androgen deficiency during late prenatal period on HSD3B expression in the fetal porcine gonads.

Pregnant sows were injected with anti-androgen flutamide (50 mg/kg bw, seven times, every day) starting at gestational day (GD) 83 or 101. The fetal gonads were obtained on GD90 or GD108. HSD3B immunolocalization was performed using rabbit polyclonal anti-mouse HSD3B antibody (provided by Prof. A H Payne from Stanford University). To assess HSD3B mRNA expression real-time PCR was carried out using the TaqMan Gene Expression Assay (Applied Biosystems).

In testes from control and flutamide-exposed fetuses, HSD3B was immunolocalized in Leydig cells. Following flutamide treatment, the number of HSD3B positive Leydig cells was higher on GD90 and lower on GD108 vs control. Moreover, flutamide administration resulted in increased HSD3B mRNA expression on GD90 and decreased HSD3B mRNA expression on GD108. In ovaries from control and flutamide-exposed fetuses, HSD3B was immunolocalized in granulosa cells of forming follicles. Following flutamide administration, increased expression of HSD3B mRNA and protein were observed on GD90. However on GD108, flutamide treatment led to decreased HSD3B mRNA expression, while no changes in the intensity of immunostaining were observed. In summary, diminished androgen action in porcine fetal gonads during late gestation induce changes in HSD3B expression, which may result in functional changes in Leydig or granulosa cells. However, it seems that androgens exert diverse biological effects depending on the gestational period.

Supported by Inventus Plus grant (IP2011 024571).

DOI: 10.1530/endoabs.32.P340

P341
Characteristics of the HIV positive transgender population of Catalonia
Ioana Patrascioiu, Carmen Quiros López, Mireia Mora Porta, Gloria Beatriz Aranda Velazquez, Felicia Alexandra Hanzu, Esther Gómez-Gili, Teresa Godàs & Irene Halperin Rabinovich
Hospital Clinic i Universitari, Barcelona, Catalonia, Spain.

Introduction
Previous studies indicate a high prevalence of HIV infection in the transgender population and associate it with sexual risk behavior, psychiatric and socio-economic problems. Anyway, few data are available regarding other factors. We assessed the prevalence of HIV and other associated characteristics in a transgender population of Catalonia.

Methods
Cross-sectional study including 234 transsexuals that started follow-up in a reference center between 2006 and 2010. Socio-demographic, clinical, anthropometrical and analytical data were collected from the medical history at baseline and after 2 years of follow-up.

Results
The prevalence of HIV was 8.5%, higher in the male-to-female than in the female-to-male transsexuals (12.6 vs 2.2%). The HIV infection was more frequent in immigrants from South/Central America (20.8%) and other countries (14.3%) than in Spanish transsexuals (4.6%). P < 0.001. There was no association with homosexuality, educational level and tobacco, alcohol or cannabis consumption. The prevalence of HIV was higher in transsexuals with a history of prostitution (26.5 vs 3.4%, P < 0.001), cocaine consumption (20 vs 5.3%, P = 0.001), heroin consumption (33.3 vs 7.5%, P = 0.009), VHC infection (55.6 vs 7.3%, P < 0.001), VHB infection (50 vs 6.4%, P < 0.001), previous hormonal treatment (17.1 vs 1.6%, P < 0.001) and sex reassignment surgery (17.5 vs 4.8%, P = 0.003). The HIV + transsexuals had higher levels of aspirate transaminase (32.1 vs 22.5 IU/L, P < 0.001), alanine transaminase (36.1 vs 23.05, P = 0.026), gamma-glutamyl transpeptidase (131.6 vs 64.4, P < 0.001), alkaline phosphatase (192.6 vs 97.09, P < 0.001), higher triglycerides (102.4 vs 81.1, P = 0.019) and lower HDL-cholesterol (39.5 vs 48.04, P = 0.004). At 2 years of follow-up there were no differences in analytical values between HIV + and HIV − transsexuals.

Conclusions
In this transgender community, the HIV infection was associated with the immigrant status, prostitution, cocaine and heroin consumption, VHC and VHB infection, previous hormonal treatment, sex reassignment surgery. Transsexuals HIV + had higher liver enzymes levels and worse lipid profile.

DOI: 10.1530/endoabs.32.P341

P342
Optimising strategies for face classification in the detection of acromegaly
Richard Frohner1, Robert P Kosiack1, Claudia Reinholz1, Dilek Gogas2, Alexander Lammert3, Rolf P Würtz4 & Harald J Schneider4
1Medizinische Klinik IV, Munich, Germany; 2School of Medicine, Marmara University, Istanbul, Turkey; 3University Medicine Mannheim, Mannheim, Germany; 4Institut für Neuroinformatik, Bochum, Germany.

Introduction
It has been shown that face classification software might help distinguishing between subjects with and without acromegaly on regular photographs. In this project, we investigated several aspects that will be necessary and helpful to bring this recognition method closer to clinical application.

Methods
Face classification was based on nodes placed on frontal and side photographs of individuals and analysis the underlying texture and geometric functions. In the first step, we analysed whether omission of nodes considered less relevant would change classification rates in the original database on 57 acromegalics and 60 controls. In a second step, we analysed how a completely new set of nodes (referring to the most common changes in morphological changes in face) will affect the classification rate. In a third step, we analysed whether classification was improved in an external data set consisting of 82 acromegalics and 141 controls for both steps.

Results
Correct classification rates in the original database were 79% with all nodes 78% if irrelevant points were omitted and 80% using the new set of nodes. Using the same approach, in the validation set, correct classification rates were 78% with all nodes (85 and 86% of acromegalics and controls, respectively) after omission of irrelevant points were omitted and 80% using the new set of nodes.

Conclusions
Reduction of nodes associated with unwanted noise can improve correct classification rates in the detection of acromegaly by face classification software.

DOI: 10.1530/endoabs.32.P342

P343
Evaluation of adults with phenylketonuria from pediatric to adult care
Montserrat Gonzalo, Antonio Omiste, Inmaculada Gonzalez & Marta Dominguez
Endocrinology and Nutrition Service Carlos Haya Hospital, Malaga, Spain.

Objective
Transition from pediatric to adult health care is a particularly vulnerable period
for patients with inborn metabolic diseases.

Our objective in this study was to evaluate the current transition of patients with phenylketonuria (PKU) in Malaga, Spain, by analysis of the metabolic control, medical care, patients satisfaction and phychosocial status.

Material and methods
We evaluate all the patients transferred to our adult unit between 2008 and 2012. Pediatric case notes and the present physician’s case notes were analyzed retrospectively.

Results
Sixteen patients (8 F/M) patients were analysed. At the time of transition, 13/16 were in good metabolic control according to current treatment guidelines. 13/16 were on a low phenylalanine diet in combination with intake of a phenylalanine free amino acid mixture. 3/16 were taking BH 4 with normal intake of proteins. 6/16 had BMI higher than 25 kg/m² (1/16 with BMI >40). 1/16 had osteopenia and 2/16 had severe osteoporosis. 8/16 carried a secondary school certificate and 3/16 had achieved university studies. 3/16 with psychopathology (all of them with late diagnosis). 3/16 were married (two women had children).

Conclusions
The patients were quite satisfied with the transitional process. During transition medical care and metabolic control were stable. The individual optimization of the therapy, established during pediatric care provides the decisive ground work for disease control in adults. It’s important to prepare, coordinate and evaluate transitional processes.

DOI: 10.1530/endoabs.32.P343

P344
Resistant hypertension: about 30 cases
Yousra Hasni, Ines Khochtali, Manel Jemel Hadiji, Hela Marmouch, Hanen Sayadi & Sylvia Mahjoub
Department of Internal Medicine and Endocrinology, Fattouma Bourguiba Hospital, Monastir, Tunisia.

Resistant hypertension (RH) is defined as blood pressure above a goal despite adherence to at least three optimally dosed antihypertensive medications of different classes, one of which is a diuretic.

Objectives
We investigated the prevalence of true resistant hypertension in our Department of Endocrinology, and we described the clincico-biological features of theses patients.

Methods
We performed a retrospective descriptive study. True resistant hypertension was diagnosed when white coat phenomenon, lack of compliance and secondary hypertension were excluded in patients with blood pressure ≥140/90 mmHg in two consecutive visits, despite to be using three blood pressure-lowering agents, including a diuretic.

Results
The sample included 30 patients (20 womens and 10 mens) among 563 patients followed in our department for hypertension.

The mean age of our patients was 54 years. Fifty percent were aged more than 65 years. Dyslipidemia was noted in 50% cases, and diabetes mellitus in 60% cases. Etiological investigation included an exploration of the aldosterone axis maded in 4. Hyperadrenocorticinism in 9 cases, urinary metanephrines in 6 cases, thyroid tests in 17 cases, renal ultrasound in 9 cases, a Doppler ultrasound of the renal arteries in 8 cases. This assessment concluded that a primary aldosteronism was found in 3 cases, an hyperthyroidism in 1 case and hyperadrenocorticism in one case. Complications associated with this (RH) were hypertensive retinopathy in 8 cases (26.6%), nephropathy in 6 cases (20%) and left ventricular hypertrophy in 7 cases (23.3%). Diuretic therapy was prescribed in 100% of cases, angiotensin-converting-enzyme inhibitor in 66.6%, an angiotensin II receptor blocker in 26.6%, a calcium channel blocker in 76.6%, a B-blocking agents in 46.6%, an alpha blocker in 13.3%, centrally acting antihypertensive agents 30% and a spironolactone in 3 cases. One patient underwent a right adrenalectomy with pathological diagnosis concluded an adrenocortical tumor.

Conclusion
Resistant hypertension is quite common. It is mainly due to the age. After confirmation of the diagnosis, it requires a thorough etiologic investigation and appropriate management.

DOI: 10.1530/endoabs.32.P344

P345
High blood pressure in young adults: 84 cases
Manel Jemel Hadiji, Yousra Hasni, Dorra Braham, Hela Marmouch, Ines Khochtali & Sylvia Mahjoub
Department of Internal Medicine and Endocrinology, Fattouma Bourguiba Hospital, Monastir, Tunisia.

Younger people with high blood pressure are 28% less likely to be diagnosed than older people. Arterial hypertension warrants further investigations to exclude secondary causes of hypertension in young people (aged <40 years).

Objectives
We conducted a retrospective descriptive study to investigate the characteristics of hospitalized hypertensive young adults (<40 years) in our department.

Results
The sample included 84 patients: 25 men (29.8%) and 59 women (70.2%). A familial history of hypertension was noted in 67.8% cases. Among all patients, headaches (30%) were the most common presenting symptom, followed by palpitations in (24%) and flushing in (2%), but the diagnosis of hypertension was fortuitous in (46%). The complications of the hypertension included hypertensive nephropathy in (23%), retinopathy in (10%), transient ischemic stroke in (7.1%) and left ventricular hypertrophy in (13%). The investigations concluded to an essential hypertension in the majority of cases (79.8%). Secondary hypertension included obstructive sleep apnea syndrome (7.1%), a primary aldosteronism (3.6%), Cushing’s syndrome (2.3%), a pheochromocytoma (1.19%), renal artery stenosis (2.3%), Basedow’s disease (1.19%), corticosurrenaloma (1.19%), macronodular adenocortical hyperplasia (1.19%).

Conclusion
Hypertension in young adults is increasing in frequency. While classic teaching dictates that secondary causes are more common in older adults, rates of essential hypertension are progressively rising. This can be explained by the high incidence of metabolic syndrome in young adults.

DOI: 10.1530/endoabs.32.P345

Diabetes
P346
Elevation of circulating free fatty acids abolishes down-regulation of skeletal muscle adiponectin receptor 1 (AdipoR1) expression caused by insulin infusion
Marek Straczkowski1,2, Monika Karczewska-Kupczewska1,2, Agnieszka Adamska3, Magdalena Stanowicz1, Natalia Matulewicz1, Izabella Kowalska1 & Agnieszka Nikolajuk1,2
1Medical University of Bialystok, Bialystok, Poland; 2Institute of Animal Reproduction and Food Research, Polish Academy of Sciences, Olsztyn, Poland.

Introduction
Adiponectin is an adipocytokine with insulin-sensitizing and anti-inflammatory properties. In skeletal muscle, it increases fatty acid oxidation and insulin-stimulated glucose uptake through binding with adiponectin receptor 1 (AdipoR1). The aim of our study was to assess the effect of insulin and Intralipid/heparin infusion on muscle AdipoR1 expression in humans.

Methods
Twenty healthy male subjects (age 25.2±3.2 years; BMI, 26.5±4.6 kg/m²) with normal glucose tolerance were studied. Six-hours euglycemic hyperinsulinemic clamp was performed two times: with and without concurrent Intralipid/heparin infusion. Indirect calorimetry was performed at baseline and every 2 h of the clamp. Biopsy of vastus lateralis muscle was performed before and after each clamp. Muscle AdipoR1 and insulin receptor substrate 1 (IRS1) mRNA expression was analyzed with Real Time PCR.

Results
Intralipid/heparin infusion resulted in a decrease in insulin sensitivity by ~40% (P<0.0001). Serum adiponectin concentration decreased similarly during both clamp (~25%, both P<0.001). Muscle AdipoR1 was positively related to serum adiponectin (r=0.46, P=0.046), insulin sensitivity (r=0.50, P=0.023), muscle IRS1 (r=0.55, P=0.014), but negatively to respiratory quotient in insulin-stimulated conditions (r=-0.45, P=0.046). Insulin infusion decreased muscle AdipoR1 expression by ~30% (P=0.006). This effect was almost completely abolished by concurrent Intralipid/heparin infusion (~7%, P=0.44;
the difference between two experiments, \( P = 0.027 \).

Conclusions
Our data indicate that elevation of circulating free fatty acids abolishes down-
regulation of muscle Adipor1 expression caused by insulin, independently of the
changes in serum adiponectin. This may be a potential compensatory mechanism
for free fatty acid-induced insulin resistance.

DOI: 10.1530/endoabs.32.P346

**P347**
Short stature, low-set ears, short 5.finger, undescended testis, bradycardia
Evrim Cakir
Department of Endocrinology and Metabolic Diseases, Amasya Sabuncuoglu Serefettin Training and Research Hospital, Amasya, Turkey.

A 22-year-old man presented to the Endocrinology unit for short stature. His
height is 1.53 cm; weight is 38.5 kg. Physical examination revealed short stature, lean
body mass, low-set ears and a short fifth finger on the right. His bone age
were consistent with 19-year. He had a history of undescended tests operation at
5-year old and history of strabismus surgery at 14-year old. He had a delta f 508
heterozygote mutation with normal sweat test. His biochemical analysis except
total and direct bilirubin, thyroid hormone levels were within normal limit.
Thrombocytopenia was occurred in the analysis of complete blood count. Platelet
count was 113 000/ml. Basal cortisol level was obtained as 455 nmol/l. Serum
FSH and LH levels were found to be increased. The FSH level was 38.4 mIU/ml
(1.5–12.4) and the LH level was 15.37 mIU/ml (1.7–8.6). The serum level of
somatomedin-C level was within normal limit for age. A sperm analyses revealed
azoosperma with 3 c amount of semen, 3–4 leukocyte and 8.2 pH. He had
normal thyroid and whole abdomen ultrasonographic findings. His scrotal
imaging was as follows; right testis was not visible due to operation, left tests
parenchyma was heterogeneous and size was 32 \( \times \) 14 \( \times \) 34 mm with no mass
imaging. The serum level of total testosterone was obtained as 5.34 ng/ml (2.49–
8.36) within normal limit. His ECG findings revealed a sinus bradycardia and
incomplete right bundle branch block. Flopsy mitral valve within 67% ejection
fraction was observed in echocardiographic evaluation. Osteoporosis was
obtained in bone mineral density measured by dual-energy X-ray absorptiometry.
Injectable testosterone esters were given. After 1 month of testosterone therapy,
the FSH level was decreased to 30.47 mIU/ml and the LH level was decreased
to 10.23 mIU/ml and the testosterone level was 5.65.

DOI: 10.1530/endoabs.32.P347

**P348**
Long-acting insulin analog exposure and cancer specific mortality in
patients with diabetes mellitus
Sorin Ioacara\(^1\), Cristian Guja\(^1\), Constantin Ionescu-Tirgoviste\(^1\),
Simona Fica\(^2\), Sorina Martin\(^2\) & Michael Roden\(^2\)
\(^1\)I. Pavel' Outpatient Clinic, Bucharest, Romania; \(^2\)Elias' Hospital,
Bucharest, Romania; \(^1\)Institute for Clinical Diabetology, German Diabetes
Center, Düsseldorf, Germany.

Aim
To test the hypothesis that exposure to insulin glargine might be associated with
increased risk of cancer mortality compared with baseline basal insulin
preparations.

Materials and methods
All consecutive diabetes patients aged over 40 years, residing in a major urban
area were screened at their first diabetes outpatient visit between 01/01/2001 and
12/31/2008 (n = 79 869). Exclusion criteria were insulin treatment at screening
(n = 14 752), no insulin treatment until 12/31/2008 (n = 55 795), <6 months of
glucose-lowering treatment alone before insulin initiation (n = 1154), insulin
prescription before glargine became available (04/17/2003, n = 1761), age < 40
or \( \geq 80 \) years at first insulin prescription (n = 406), <6 months of insulin
treatment following insulin initiation. A total 4990 subjects were followed-up for
death based on death certificate, until 12/31/2011, using data from National
Institute of Statistics. Baseline was defined at 6 months after insulin initiation.
Antidiabetic prescriptions were available. Adjusted time-dependent competing
risk regression analysis, with daily updates of treatment modalities was
performed. Simultaneously use of cumulative exposure and ever exposed term
of the available treatment options, a ‘fixed’ cohort, cumulative exposure limited
to that attained 1 year prior to death (minimizing the reverse causation), and a
propensity score analysis completed the evaluation.

Results
Mean baseline age was 62 ± 9 years, and follow-up 4.7 ± 1.9 years (23 179
person-years). Glargine cumulative dose exposure significantly lowered cancer
mortality risk, subhazard ratio (SHR) 0.94 (95% CI 0.89–0.99, \( P = 0.033 \)).
Cumulative exposure limited to that attained 1 year prior to death showed a
sharply cumulative exposure time SHR 0.94 (95% CI 0.89–0.99, \( P = 0.018 \)) and
cumulative dose SHR 0.92 (95% CI 0.86–0.98, \( P = 0.014 \)). Glargine use
was associated with cumulative exposure time and cumulative dose that were
significant predictors for lower pancreatic and breast cancer mortality, but with no
impact on lung, colorectal, female genital, liver, and urinary tract cancer deaths.

Conclusions
The cumulative dose exposure to insulin glargine was associated with a lower risk
of cancer mortality in general, and of breast and pancreatic cancer in particular.
No glargine associated ‘harm’ was found even after additional ‘fixed’ cohort
or propensity score analyses were performed.

DOI: 10.1530/endoabs.32.P348

**P349**
Expression of adiponectin gene and adiponectin receptors in placental
and adipose tissue in women with gestational diabetes mellitus
Beata Mattijaszek-Matuszek\(^1\), Mariusz Kowalczyk\(^1\), Agnieszka Łagowska-
Batrya\(^2\), Wojciech Gerland\(^2\), Andrzej Nowakowski\(^1\), Bozena Leszczynska-
Gorzelak\(^3\) & Janusz Kocki\(^4\)
\(^1\)Department of Endocrinology, Medical University, Lublin, Poland;
\(^2\)Medical Laboratory LOMA, Opole, Poland; \(^3\)Department of Obstetrics and
Perinatology, Medical University, Lublin, Poland; \(^4\)Department of Clinical
Genetics, Medical University, Lublin, Poland.

Introduction
Adiponectin shows its beneficial insulin-sensitizing properties, however, women
with gestational diabetes mellitus (GDM) present hypoadiponectinemia.

Aim of the study
To assess the expression of adiponectin gene as well as its AdipoR1 and AdipoR2
receptors in placenta and adipose tissue and to determine potential correlations
with chosen metabolic parameters (clinical and biochemical).

Patients and methods
Thirty-six pregnant women, who for obstetric reasons underwent cesarean
sections, were divided into two groups. The study group included 20 women
diagnosed with GDM by routine prenatal tests, whereas the control group
comprised 16 women with normal oral glucose tolerance test (OGTT).
Intrapartum and subcutaneous adipose tissue samples were obtained
intraoperatively from all women, whereas the placental samples were obtained
straight after delivery. Adiponectin, AdipoR1 and AdipoR2 gene expressions
were assessed using the r-PCR method.

Results
Serum glucose and insulin concentrations, HOMA-IR and HOMA-B levels
were significantly higher in the GDM group, whereas the QUICKI values
were respectively lower. Adiponectin concentrations were significantly lower
in the study group than in the control one 4.9 ng/ml (4.4–5.8) vs 5.9 ng/ml
(5.1–8.0 ng/ml). The expression of AdipoR1 receptor was significantly higher in
the study group, whereas there was no significant difference between the
expression of adiponectin and AdipoR2 receptors between the groups.

Conclusion
Impaired glucose tolerance in women with GDM modifies the expression of
AdipoR1 in placenta and adipose tissue, but it does not affect the level of
expression of adiponectin mRNA and AdipoR2.

DOI: 10.1530/endoabs.32.P349

*Endocrine Abstracts (2013) Vol 32*
**P350**

**Effects of Vaspin on expressions of NF-κB and its target genes in endothelial EA.hy926 cells**

Shiwei Liu, Kun Yang, Xiaojin Chen & Shujun Zhao
Shanxi Dayi Hospital, Taiyuan, Shanxi, China.

Introduction
The visceral adipose tissue-derived serine protease inhibitor (vaspin), a novel adipocytokine, has been widely reported to be associated with obesity and insulin resistance. Obesity induced chronic inflammatory process plays a pivotal role in insulin resistance and is characterized by the activation of NF-κB pathway and its target genes. The present study aims to investigate the effects of vaspin on NF-κB pathway and its target genes in basal and TNF-α-stimulated endothelial EA.hy926 cells to further elucidate the role of vaspin in the development of obesity and insulin resistance, which may provide diagnostic and therapeutic strategies in the treatment of obesity and insulin resistance correlated disorders, such as type-2 diabetes and metabolic syndrome.

Materials and methods
In this study, we constructed a NF-κB luciferase reporter system and stably transfected endothelial EA.hy926 cells with reporter plasmid pNFκB-luc. Following transfection, basal and TNF-α-stimulated EA.hy926 cells were treated with various concentrations of vaspin (0–3200 ng/ml). Luciferase activity assay was used to determine the transcription activities of NF-κB. Expressions of target genes ICAM-1, VCAM-1 and MCP-1 were measured by real-time fluorescence quantitative PCR and western-blot in mRNA and protein levels.

Results
Results showed that vaspin significantly activated the expression of NF-κB in transfected EA.hy926 cells in a dose-dependent manner (P < 0.05). Levels of ICAM-1, VCAM-1 and MCP-1 were significantly increased by the treatment of EA.hy926 cells with vaspin (> 200 ng/ml) or TNF-α (10 ng/ml), which can both be obviously reversed by the use of NF-κB inhibitor Bay 11-7082 (10 μM) (P < 0.05). However, vaspin inhibited the TNF-α induced activation of NF-κB in a dose- and time-dependent manner (P < 0.05).

Conclusions
Vaspin activated the expression of NF-κB and its target genes but inhibited TNF-α induced activation of NF-κB, indicating a dual role of vaspin in NF-κB pathway in human vascular endothelial cells and a potential mechanism in the regulation of inflammation in insulin-resistance.

DOI: 10.1530/endoabs.32.P350

**P351**

**Skeletal muscle and adipose tissue glycoprotein 130 expression is associated with insulin resistance in humans**

Monika Karczewska-Kupczewska1,2, Agnieszka Nikolausk1,2, Agnieszka Adamksa1, Natalia Matulewicz1, Magdalena Stefanoewicz1, Irina Kowalska1 & Marek Straczkowski1,2

1University of Białystok, Białystok, Poland; 2Institute of Animal Reproduction and Food Research, Polish Academy of Sciences, Olsztyn, Poland.

Introduction
Glycoprotein 130 (gp130), like interleukin 6 (IL6), acts through plasma membrane receptors consisting of two glycoproteins: a cytokine binding subunit (like IL6R) and gp130, responsible for signal transduction. IL6 may regulate insulin sensitivity in a dual manner, as both insulin-sensitizing and -desensitizing actions have been reported. Other gp130 cytokines may have a beneficial metabolic effects. The aim of the present study was to assess skeletal muscle and adipose tissue IL6R and gp130 expression in relation to insulin sensitivity and obesity in male subjects.

Methods
We examined 86 young (age 23.22 ± 4.11 years), apparently healthy male subjects with normal glucose tolerance, 45 lean (BMI below 25 kg/m²) and 41 with overweight or obesity (BMI between 25 and 40 kg/m²). Euglycemic hyperinsulinemic clamp, indirect calorimetry and biopsies of vastus lateralis (12.4 vs 6.6%). Nonetheless, fewer in the elevated CRP group were on insulin treatment (7.7 vs 5.0%, P < 0.001), and were less likely to do regular sports activities (30.8 vs 46.3%, prevalence ratio 0.67 (95% CI 0.47–0.86). They also had a higher median HbA1C (7.4 vs 6.6%, P < 0.001), higher fasting blood glucose (7.26 vs 6.82 mmol/l, P < 0.001), and waist circumference (113 vs 100 cm, P < 0.001), and were more likely to be on insulin treatment (7.7 vs 5%, prevalence ratio 1.54 (95% CI 0.96–2.13). Blood pressure, lipids, and current smoking were similar between groups. Patients with high CRP had higher Charlson comorbidity index scores (score ≥ 1 in 35.2 vs 26.1%) and more previous cardiovascular disease (20.4 vs 16.9%) and chronic pulmonary disease (12.4 vs 6.6%). Nonetheless, fewer in the elevated CRP group were on statin therapy (58.9 vs 69.3%).

Conclusions
Among newly diagnosed T2D patients in Denmark, 16.9% had CRP values of more than 6 mg/l. Patients in the highest CRP tertile were more likely to be female, obese, physically inactive, and comorbid, with worse blood glucose control compared to those with low CRP.

DOI: 10.1530/endoabs.32.P352

**P352**

**Increased alanine aminotransferase levels and associated characteristics among newly diagnosed type 2 diabetes patients: results from the DD2 study**

Reimar Thomsen1, Anil Mor1, Jørgen Rungby2, Sinna Ulrichsen2, Jens Nielsen2, Jacob Stidsen3, Søren Friisborg1, Ivan Brandslund2, Jens Christiansen, Henning Beck-Nielsen2 & Henrik Sørensen1

1Aarhus University Hospital, Aarhus, Denmark; 2Aarhus University, Aarhus, Denmark; 3Odense University Hospital, Odense, Denmark; 4Lillebaelt Hospital, Vejle, Denmark.

Objectives
There is limited knowledge of high-sensitivity C-reactive protein (CRP) levels among newly diagnosed T2D patients in the population-based setting, and of factors associated with elevated CRP.

Methods
Measurements of CRP were performed in the first 1036 T2D patients in the nationwide DD2 project, enrolling new T2D patients from general practitioners and hospital specialist outpatient clinics. We examined the number of T2D patients within CRP tertiles and clinically relevant cutoff points of CRP (≤ 1.0, 1.0–2.99, 3.0–5.99, or ≥ 6.0 mg/l), and demographic, clinical, and lifestyle characteristics associated with elevated CRP.

Results
Median CRP was 2.1 mg/l (inter-tile range, 1.3–5.6 mg/l). 20.6% of patients had a CRP level of 3.0–5.99 mg/l and 19.6% had a CRP of ≥ 6 mg/l. As compared to the 361 people with CRP values in the lowest tertile (≤ 1.3 mg/l), those with CRP values in the highest tertile (> 6.6 mg/l) were younger (median age 58 vs 62 years, P < 0.0001) and more likely to be female (52.7 vs 39.3%, prevalence ratio 1.34 (95% CI 1.18–1.50)). Patients in the highest CRP tertile had substantially higher median values of BMI (34 vs 28.7 kg/m², P < 0.001) and waist circumference (113 vs 100 cm, P < 0.001), and were less likely to do regular sports activities (30.8 vs 46.3%, prevalence ratio 0.67 (95% CI 0.47–0.86). They also had a higher median HbA1C (7.4 vs 6.6%, P < 0.001), higher fasting blood glucose (7.26 vs 6.82 mmol/l, P < 0.001), higher C-peptide (784 vs 545, P < 0.0001), and were more likely to be on insulin treatment (7.7 vs 5%, prevalence ratio 1.54 (95% CI 0.96–2.13). Blood pressure, lipids, and current smoking were similar between groups. Patients with high CRP had higher Charlson comorbidity index scores (score ≥ 1 in 35.2 vs 26.1%) and more previous cardiovascular disease (20.4 vs 16.9%) and chronic pulmonary disease (12.4 vs 6.6%).

Conclusions
Among newly diagnosed T2D patients in Denmark, 19.6% had CRP values of more than 6 mg/l. Patients in the highest CRP tertile were more likely to be female, obese, physically inactive, and comorbid, with worse blood glucose control compared to those with low CRP.

DOI: 10.1530/endoabs.32.P353

**P353**

**Autoantibodies to the insulin- and IGF1-receptor in human sera**

Tim Welsink1,2, Christian Schwiebert3, Waldemar Minich1 & Lutz Schomburg1

1Institute for Experimental Endocrinology, Charité Universitätmedizin Berlin, Berlin, Germany; 2ICI immunochemical Intelligence GmbH, Berlin, Germany; 3InVivo BioTech Services GmbH, Hemmigsdorf, Germany.

Introduction
Autoantibodies (aAB) are characteristic of autoimmune diseases, but may also be found in apparently healthy individuals and precede pathological symptoms. We have recently reported on autoantibodies against the IGF1-receptor (IGF1R-aAB) in diabetic subjects and patients with Graves’ disease (1). The isolated aAB were able to immunoprecipitate the recombinant autoantigen and antagonized IGF1 signaling in vitro. Given the structural similarities between IGF1R and insulin

Endocrine Abstracts (2013) Vol 32
P354
Physiological role for Angptl4/fiaf in exercise-induced muscle AMPK activation
Min-Seon Kim1, Ghi-Su Kim1, Hyuckki Chang2, Mi-Seon Shin1 & Hyun Kyong Kim1
1Asan Medical Center, Seoul, Republic of Korea; 2Seoul Women’s University, Seoul, Republic of Korea.

Introduction
Angiopoietin-like protein 4 (Angptl4), also known as fast-induced adipose factor (Fiaf), is a glycoprotein which is known as a potent inhibitor of lipoprotein lipase. We have reported that hypothalamic Angptl4 is a novel anorexigenic molecule by inhibiting hypothalamic AMPK activity. In the present study, we investigated a potential role of Angptl4 in exercise-related physiology.

Methods
We determined changes in Angptl4 mRNA/protein levels along with phospho-total AMPK levels in leg skeletal muscle of mice following moderate strength prolonged running exercise (18 m/min for 50 min). We treated Angptl4 peptide in C2C12 skeletal muscle cells to test if Angptl4 can activate AMPK activity in skeletal muscle. Finally, we compared the effects of chronic running exercise (5–18 m/min for 50 min, five times/week for 2 weeks) on muscle AMPK activity and food intake of Angptl4 null mice and their wild littermates.

Results
Running exercise significantly increased Angptl4 mRNA and protein levels and AMPK phosphorylation in skeletal muscle. Treatment of Angptl4 in C2C12 cells significantly increased AMPK and ACC phosphorylation in a dose- and time-dependent manner. Exercise-induced AMPK activation in skeletal muscle was diminished in Angptl4 null mice. Chronic running exercise significantly reduced food intake in wild mice, but exercise-induced anorexigenic effect were blunted in Angptl4 null mice.

Conclusion
Our data have demonstrated a potential role of skeletal muscle Angptl4 in exercise-induced AMPK activation and exercise induced anorexia. Therefore, Angptl4 may mediate metabolic changes during exercise.

DOI: 10.1530/endoboa.32.P354

P356
Risk factors for impaired glucose tolerance and diabetes mellitus after liver transplantation
Guillermo Martinez1,2, Gonzalo Allo1, Ana Fernández2, Mercedes Aramendi1, Carlos Jiménez2, Enrique Moreno1,2 & Federico Hawkins1,2
1Hospital Universitario 12 de Octubre, Madrid, Spain; 2Universidad Complutense, Madrid, Spain.

Risk factors involved in new-onset diabetes mellitus after transplantation (NODAT) remain unclear. Clinical studies have demonstrated the association between low vitamin D levels with insulin resistance and diabetes. In animal models, osteocalcin deficiency leads to high glucose levels and insulin resistance. The aim of this study is to evaluate the prevalence of NODAT and other alterations of glucose metabolism after liver transplantation (LT) at our institution. Also, we assess the relationship between serum osteocalcin, 25-OH vitamin D levels and NODAT. Influence of hepatitis C virus (HCV) infection was also studied.

Methods
In the period 2011–2012, 133 LT patients (90 men and 43 women) with a mean age of 58.5 years were studied. None of them had been diagnosed of diabetes prior to transplant. Minimum period posttransplantation was 6 months and mean follow-up was 9.2 years. 75 g oral glucose tolerance test (OGTT) was performed to assess glucose, insulin and C-peptide levels at baseline, and 60 and 120 min. Data on medical history, anthropometric measurements and lab test (including HbA1c, total osteocalcin, and 25-OH vitamin D levels) were collected. 2011 ADA diagnostic criteria were used.

Results
Thirty four patients developed diabetes or were treated with insulin or oral antidiabetic medication. OGTT was performed in 99 patients: 12.1% had NODAT criteria, and 32.3% showed impaired glucose tolerance (IGT). 30.3% showed vitamin D deficiency (< 20 ng/ml). No significant differences were observed in osteocalcin and vitamin D levels between NODAT, IGT, and normal. No correlation was found between osteocalcin and glucose, insulin, C-peptide, or HbA1c. HOMA-IR was significantly higher in diabetic (P < 0.001) than in normals. QUICKI was significantly lower in prediabetic (P < 0.05) and diabetic (P < 0.001) compared with normal. HCV positive status (before and after transplantation) was associated with diabetes onset (P = 0.05 and 0.001 respectively).

Conclusion
Prevalence of NODAT and IGT is high in LT recipients. Our study didn’t find

P355
Predictive value of HbA1c and glucose fluctuations in hypoglycemia risk in patients with type 1 diabetes
Daniela Guelho, Luísa Barros, Carla Baptista, Isabel Paiva, Sofia Gouveia, Joana Saraiva, Carolina Moreno & Francisco Carrilho
Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal.

Introduction
Many patients with diabetes experience high variability in glucose concentrations which is associated with a risk of hypoglycemia. The aim of this was to compare the predictive value of HbA1c, mean interstitial glucose (MIG), and glucose variability (GV) in the risk of hypoglycemia in patients with type 1 diabetes (T1D).

Methods
Continuous glucose monitoring, using CGMS system, was performed in 130 T1D patients with diabetes duration of 17.1 ± 8.6 years, in intensive insulin therapy (49.8 ± 17.9 IU). MIG (in mg/dl), GV measured by standard deviation of MIG (mg/dl), time per day spent in hypoglycemia (HT), interstitial glucose ≤ 70 mg/dl (h), and episodes of nocturnal hypoglycemia (NH), hypoglycemia between midnight and 0800 h, in %, were assessed. Patients were divided in group I (n = 84) with HbA1c ≤ 7.5%, and group II (n = 46) with HbA1c > 7.5%.

Results
Group I presented a significantly lower MIG (139.2 ± 25.9 vs 173.1 ± 33.2 mg/dl, P < 0.05) and GV (58.4 ± 18.8 vs 70.3 ± 18.6 mg/dl, P < 0.05) and more HT (1.85 ± 1.68 vs 1.9 ± 1.04 h, P < 0.05). NH episodes weren’t significantly different between groups (8.7 ± 4.8%). HT was positively correlated with GV (r = 0.23, P = 0.01) and negatively with HbA1c and MIG (r = −0.23 and r = −0.36, P = 0.01). NH was correlated with MIG (r = −0.24, P < 0.05).

Conclusions
Group I patients presented lower MIG and GV, and more HT than group II. NH episodes weren’t significantly different between groups. An elevated HbA1c wasn’t a reliable indicator of lower risk of hypoglycemia. GV independently predicts daily time duration spent in hypoglycemia.

DOI: 10.1530/endoboa.32.P355

Endocrine Abstracts (2013) Vol 32

15th European Congress of Endocrinology 2013
osteocalcin and vitamin D levels as predisposing factors for the onset of both conditions. Hepatitis C virus infection increased the risk of NODAT.

DOI: 10.1530/endoabs.32.P356

P357
Acute exercise leads to increased HbA1c and fructosamine levels in athletes with type 1 diabetes

Luis Forga1, María José Gutiér1, Laura Chinchurreta1, Francisco Javier Lafiña1, Ana Iriarte1 & José Manuel Fernández-Real2
1Complejo Hospitalario de Navarra, Pamplona, Spain; 2Hospital Universitario de Girona Josep Trueta, Girona, Spain.

Introduction
In patients with type 1 diabetes, exercise has not consistently been shown to improve glycaemic control, as measured using HbA1c levels. Participation in competitive sports may even worsen glycaemic control. Free radicals and oxidative stress markers are known to increase during acute exercise in parallel to decreased circulating antioxidant concentrations. We aimed to analyze the effects of chronic and acute exercise on circulating HbA1c and fructosamine levels.

Design
We evaluated six patients (five men and one woman). Their mean age was 41.8 (range 22–49). Their mean diabetes duration was 11.3 years (range: 5–20). All of them were under intensive treatment before the study (four with MID and two with ISCI). Prior to the training period, they usually ran 35 km 3 days every week, which increased to 70–80 km 5 days/week during the training period. We analyzed their HbA1c and fructosamine levels before and after the training period and also before and after running a half-marathon (20 km).

Results
After eight months training, mean HbA1c decreased from 7.80% (95% CI 6.80–8.87) to 7.55% (95% CI 6.52–8.87) (P = 0.13) and mean fructosamine levels decreased from 370.5 μmol/l (95% CI 311.8–429.12) to 350 μmol/l (95% CI 292.97–407.02) (P = 0.075). Paradoxically, after acute exercise, mean HbA1c increased from 7.53% (95% CI 6.54–8.52) to 7.61% (95% CI 6.61–8.51) (P = 0.025) in parallel to raised fructosamine levels from 348.3 μmol/l (95% CI 298.1–398.5) to 363.8 μmol/l (95% CI 318.3–409.2) (P = 0.046). HbA1c was determined using HPLC (reference range: 4.1–6.2%). Intra and interassay coefficients of variation (CV) were 0.7 and 0.74% respectively. Fructosamine was determined by spectrophotometer (normal values ≤285 μmol/l). Intra and interassay CV were 1.7 and 3.9% respectively.

Conclusion
Acute exercise should be taken into account as one of the factors influencing HbA1c variability in a short time.

DOI: 10.1530/endoabs.32.P357

P358
Increased alanine aminotransferase levels and associated characteristics among newly diagnosed type 2 diabetes patients: results from the DD2 study

Anil Mor1, Reimar Thomsen1, Jørgen Rungby2, Sinna Ulrichsen1, Jens Nielsen3, Jacob Südsen4, Søren Friiborg1, Ivan Brandslund6, Jens Christiansen5, Henning Beck-Nielsen7 & Henrik Svendsen1
1Aarhus University Hospital, Aarhus, Denmark; 2Aarhus University, Aarhus, Denmark; 3Odense University Hospital, Odense, Denmark; 4Lillebaelt Hospital, Vejle, Denmark.

Objectives
Elevated levels of serum alanine aminotransferase (ALT) have been linked with non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), insulin resistance and the metabolic syndrome in type 2 diabetes (T2D) patients. We examined ALT levels in newly diagnosed T2D patients, and the factors associated with such elevation.

Methods
Measurements of ALT were performed in 1025 (43% women and 57% men) new T2D patients enrolled from general practitioners and hospital specialist outpatient clinics in the nationwide DD2 project. We calculated the median value of ALT, and examined the number of T2D patients within gender specific quartiles of ALT values. We also examined demographic, clinical, and lifestyle characteristics associated with increased ALT levels. Data on BMI, lipid profile and blood pressure could be ascertained from the Danish Diabetes Database for Adults for a subgroup (n = 525) of the study population.

Results
The median value of ALT was 24 IU/l (inter-quartile range 18–32 IU/l) in women and 30 IU/l (inter-quartile range 22–41 IU/l) in men. 26% were in the lowest ALT quartile (<18 IU/l for women and <22 IU/l for men, respectively) and 24% were in the highest ALT quartile (>32 IU/l/41 IU/l for women/men). As compared to people with ALT values in the lowest quartile, those with high ALT were younger (median age 57 vs 64 years, P < 0.0001), more obese (median BMI 31.2 vs 29.1 kg/m², P = 0.004), and had a larger waist circumference (111 vs 101 cm, P < 0.0001) and higher median CRP levels (2.8 vs 1.8 mg/l, P = 0.0147). They also had substantially poorer glucose control (HbA1c 7.40 vs 6.90%, P = 0.084; fasting blood glucose 7.56 vs 6.86 mmol/l, P < 0.0001), and a worse lipid profile (total-cholesterol 4.70 vs 4.15 mmol/l, P = 0.006), whereas blood pressure was similar between groups. Patients in the highest ALT quartile had more alcohol overuse (10.4 vs 2.2% with >14/21 weekly drinks in women/men, P < 0.0001) as compared to subjects in the lowest quartile.

Conclusions
Among newly diagnosed T2D patients, those with a high ALT level were younger, had more abdominal obesity, dyslipidemia, poorer glucose control, more alcohol overuse, and higher CRP levels as compared with those in the lowest ALT quartile.

DOI: 10.1530/endoabs.32.P358

P359
Reconsidering guidance for postnatal glucose screening in gestational diabetes

Sheba Jarvis1,2, Christine Feben2, Stephanie Roy2, Richard Sheridan2, Tony Bore1, Orla Trainer1 & Michael R Clements1
1Imperial College London, Hammersmith Hospital, London, UK; 2Watford General Hospital, Vicarage Road, Watford, UK.

Background
National Institute for Health and Clinical Excellence (NICE) guidelines advise that GDM be diagnosed using a 2-h 75 g oral glucose tolerance test (OGTT). However there is lack of consensus on the optimal postpartum surveillance. Current postpartum screening guidance suggests a single fasting plasma glucose (FPG) at 6-weeks with annual testing thereafter. As women with GDM are often from mixed ethnic groups and frequently have postprandial hyperglycaemia, a 2-h OGTT result may be more relevant.

Objectives
Our study assessed if postpartum screening using FPG alone missed significant numbers of patients with pre-diabetes or impaired glucose tolerance (IGT).

Methods
Retrospective analysis of 211 women diagnosed with GDM over a 4-year period was undertaken. All pregnant women had a plasma glucose screen at booking and 28 weeks. OGTT was undertaken if FPG was >6.0 mmol/l or random plasma glucose was ≥7 mmol/l, and also in the presence of glycosuria or major clinical risk factors. All patients were invited for a postnatal OGTT at 6-weeks postpartum.

Results
12 788 mothers were subject to plasma glucose screening in pregnancy. GDM was diagnosed on OGTT if FPG was >6.0 mmol/l or 2-h value was ≥7.8 mmol/l and the incidence was 1.65%. In 33 women a FPG >6.0 mmol/l was observed (7.62±0.76 mmol/l, mean±s.e.m.) and all patients had elevated 2-h values ≥7.8 mmol/l (9.79±0.01). 79% of women attended for postnatal OGTT. 6 women had frank diabetes and 12% had impaired glucose tolerance (2-h value 9.30±0.06 mmol/l) which would have been missed on FPG alone.

Conclusion
GDM was diagnosed most commonly on elevated 2-h glucose rather than FPG. Using FPG alone for postnatal screening misses a substantial number of cases of diabetes.
women with persisting IGT. As post-prandial hyperglycaemia is associated with increased cardiovascular risk, lifestyle advice and closer surveillance is required.

**P360**

**TCF7L2** gene polymorphisms may influence insulin sensitivity and leptin levels independently from BMI and body fat content

Adam Kretowski, Edyta Adamaska, Natalia Wawrusiewicz-Kurylewicz, Anna Ciko, Joanna Gosciak, Katarzyna Maliszewska, Juliusz Wilk, Magdalena Wasczeniuk, Danuta Lipinska, Justyna Pliszka, Michal Ciborowski & Maria Gorska

1 Department of Endocrinology, Diabetology and Internal Medicine, Medical University of Bialystok, Bialystok, Poland; 2 Centre for Clinical Research, Medical University of Bialystok, Bialystok, Poland; 3 Centre for Experimental Medicine, Medical University of Bialystok, Bialystok, Poland; 4 Department of Software Engineering, Bialystok Technical University, Bialystok, Poland; 5 Department of Dietetics and Clinical Nutrition, Medical University of Bialystok, Bialystok, Poland.

**Introduction**

The genome-wide association studies have recently expanded the number of genetic susceptibility loci for type 2 diabetes and obesity. Transcription factor 7-like 2 (**TCF7L2**) gene seems to be one of the most predictive identifiable factors promoting T2DM development. It has been suggested that TCF7L2 influences pancreatic β-cell function but the effect of genetic variants of **TCF7L2** on metabolic syndrome development is not well characterized among subjects with obesity. The aim of our study was to analyze whether genetic variants of the **TCF7L2** gene influence fasting leptin levels and insulin sensitivity in nondiabetic obese/overweight subjects.

**Methods**

We genotyped previously identified **TCF7L2** SNPs: rs7901695 and rs7903146 in 944 subjects (463 women and 481 men), who underwent anthropometry (BMI) and body composition analysis: percent of body fat, visceral, and subcutaneous abdominal adipose tissue by multi-frequency bio-impedance method.

**Results**

In the present study we found that subjects with TT rs7903146 **TCF7L2** homozygotes presented significantly higher fasting levels of leptin (29.77 vs 19.7 ng/ml, *P*<0.035) and higher HOMA-IR (3.93 vs 2.6, *P*<0.009), despite the lack of differences in BMI, body fat content, and body fat distribution. Moreover in the logistic regression analysis presence of CC genotype of rs7901695 **TCF7L2** predicted higher IR independently from BMI, gender and caloric intake (*P*<0.01).

**Conclusions**

We believe that our study may help to understand the pathways that **TCF7L2** gene influence the risk of T2DM and provide personalized treatments and prevention strategies to fight against type 2 diabetes.

**DOI:** 10.1530/endoabs.32.P360

**P361**

**Type 2 diabetes and prostate cancer risk in Korean men with low PSA**

Hee-In Kim, Jang Soo Cho & Hee-Jin Ha

Institute for Health Promotion and Department of Epidemiology and Health Promotion, Graduate School of Public Health, Yonsei University, Seoul, Republic of Korea.

**Introduction**

Diabetes as a risk factor of cancer should be explored further. The value of PSA is limited because we cannot exclude prostate cancer in lower PSA levels. We limited because we cannot exclude prostate cancer in lower PSA levels. We

**Method**

A total of 179,456 health examinees (men, aged 30–89 years) from 1994 to 2010 were participated. Participants with any cancer or potential prostate diseases were excluded from analysis. Prostate cancer incidence/death outcome was collected from hospital admission records due to prostate cancer from 2002 to 2010. Result

Serum PSA measurements were divided into seven levels: Q1, 0–0.56; Q2, 0.57–0.79; Q3, 0.80–1.19; Q4, 1.20–2.50; Q5, 2.51–4.00; Q6, 4.01–10.00; and Q7, 10.01–20.00 ng/ml. The mean age was 422 within Q1–Q4 and 594 in participants with PSA higher than 2.5 ng/ml. In Q5–7, the prevalence of diabetes was higher than Q1–4 (*P* for trend <.0001). In Cox proportional hazard models, participants in Q4 showed higher hazard ratios with prostate cancer incidence after adjustment for multiple confounding factors compared to the Q1 group, though they were within the usual normal range. Participants in Q3 and Q4 with PSA lower than 2.50 ng/ml showed significantly higher HRs (Hazard ratio (HR) 6.34, 95% CI 4.40–9.15 in Q4; HR 1.61, 95% CI 1.01–2.45 in Q3).

**Conclusion**

These findings suggest that examinees with lower PSA than 2.5 might need to be followed up, particularly in diabetes (This study was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology, 14 245 and by the Korea government (MEST) (2011-0029348).

**DOI:** 10.1530/endoabs.32.P361

**P362**

**The association between severity of impaired glucose tolerance in gestational diabetes with age, BMI, and ethnicity in the UK**

Benjamin Jones, Satthyan Balaji & Christine Cotzias

West Middlesex University Hospital, Isleworth, London, UK.

**Introduction**

Gestational diabetes (GDM) has been shown to cause adverse fetal outcomes including macrosomia, shoulder dystocia and stillbirth. The multinational Hyperglycaemia and Pregnancy Outcome (HAPO) Study has shown there is a linear relationship between OGTT result and fetal growth. Investigating epidemiological risk factors is essential to ensure appropriate high-risk groups are being screened.

**Methods and materials**

A retrospective case note review was undertaken of all patients with newly diagnosed GDM (n=321) over a 2-year period at the West Middlesex University Hospital. The 75 g OGTT results were recorded with relevant demographic data including parity, age, BMI, and ethnicity.

**Results**

Asian ethnicity had the highest fasting plasma glucose (*μ* = 5.49; *n* = 206) and 2-h plasma glucose (*μ* = 9.32; *n* = 208). One-way ANOVA revealed a statistically significant difference between Caucasian, Black, Asian, and Oriental ethnicities with fasting glucose (*P* = 0.008) and at 2 h (*P* = 0.046). Regression analysis revealed a significant direct association between BMI and fasting glucose (*P* = 0.002; *R* = 0.169). On simple scatter plot analysis, an inverse correlation was evident between age and fasting plasma glucose level, although this was not significant on regression analysis.

**Discussion**

This study highlights the variation in glucose tolerance between different ethnicities. It also substantiates the known relationship between BMI and fasting plasma glucose. Historically increasing age has been associated with insulin resistance and is a known risk factor for GDM. Interestingly, this study suggests that fasting glucose amongst GDM patients is inversely related to age, perhaps owing to lifestyle factors and differing perceptions amongst younger patients.

**DOI:** 10.1530/endoabs.32.P362

**P363**

**High prevalence of elevated liver transaminases among 38 727 patients in a diabetes centre in the United Arab Emirates**

Zara Hannoun, Nader Lessan & Mahla T Barakat

Imperial College London Diabetes Centre, Abu Dhabi, United Arab Emirates.

**Introduction**

Liver transaminases are markers of parenchymal liver disease, most commonly non-alcoholic steatohepatitis (NASH), the inflammatory component of non-alcoholic fatty liver disease (NAFLD). Common causes include obesity and type 2 diabetes mellitus (T2DM), both common conditions in the UAE. The prevalence of NAFLD in this population is not known. We report data from a large diabetes centre including ALT and aspartate transaminase (AST) levels in patients with and without diabetes.

**Methods**

ICLDC adult patient database (n = 38,727) was accessed to obtain information on liver transaminase (ALT or AST). These are normally requested as part of the investigation of patients with diabetes mellitus, hyperlipidaemia and other conditions. Patients with AST or ALT over five times the upper limit of normal were excluded from the analysis (n = 99). Other relevant parameters on patients’

**Endocrine Abstracts (2013) Vol 32**
last medical consultation were also analysed.

Results
38 727 out of a total of 61 184 patients (normal glucose tolerance in 13.7%, T2DM in 41.8% and T1DM in 2.1%) over the age of 18 years had liver transaminase levels available. Elevated ALT and AST were noted in 20.0% (n = 7771) and 12.0% (n = 4643) of patients respectively. Both enzymes were elevated in 9.66% (n = 3752) of patients. Mean ALT and AST were 25.5 ± 17.1 and 22.6 ± 9.9 U/L respectively with no statistically significant difference in different weight groups and glucose tolerance categories. There was no significant correlation between waist to hip ratio and ALT or AST in patients regardless of glucose tolerance status.

Conclusions
Elevated liver transaminases are common in the population studied. Weight, abdominal obesity or glucose tolerance status did not appear to be important determinants of this rise. This suggests that conventional markers of body habitus, which are used in European populations, are less valid in the UAE as predictors of the presence of fatty liver.

DOI: 10.1530/endoabs.32.P363

P364
Heterozygous deficiency of endoglin decreases insulin and hepatic triglyceride levels during high fat diet
Daniel Beiroa,1 Romero-Piñó Amparo,2 Langa Carmen,a Bernabeu Carmelo,b Lopez Miguel,1 Jose M Lopez-Novoa,3 Negrias Ruben1 de Noghez Carlos1
1Department of Physiology, Instituto de Investigaciones Sanitarias (IDIS), CIBER Fisiopatologia de la Obesidad y Nutricion (CIBERObn), School of Medicine-CIMUS, Santiago de Compostela, Spain; 2Centro de Investigaciones Biologicas, Consejo Superior de Investigaciones Científicas (CSIC), and Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Madrid, Spain; 3Renal and Cardiovascular Physiopathology Unit, Department of Physiology and Pharmacology, University of Salamanca and Instituto de Investigaciones Biomédicas de Salamanca (IBSAL), Salamanca, Spain.

Introduction
Endoglin is a transmembrane auxiliary receptor for transforming growth factor-β (TGF-β) that is predominantly expressed on proliferating endothelial cells. It plays a wide range of physiological roles but its importance on energy balance or insulin sensitivity has been unexplored.

Material and methods
Heterozygous deficient mice (HZ) were fed standard chow or high fat diet during postnatal day 10-70. Heterozygous deficient mice (HZ) were fed standard chow or high fat diet during postnatal day 10-70. Heterozygous deficiency of endoglin plays a wide range of physiological roles but its importance on energy balance or insulin sensitivity has been unexplored.

Results
Liver triglyceride levels was measured using colorimetric methods. Liver triglyceride levels was measured using colorimetric methods. Liver triglyceride levels was measured using colorimetric methods.

Conclusion
Here we report for first time that heterozygous endoglin deficiency in mice decreases high fat diet-induced hepatic triglyceride content and insulin levels these effects are independent of changes in body weight or adiposity. At molecular level, we failed to detect relevant changes in the insulin signalling pathway. We found decreased triglyceride content in the liver of endoglin heterozygous mice fed a high fat diet.

P365
Prediabetes in human immunodeficiency virus-infected patients: prevalence and clinical significance
Carolina García-Figueraa,1, Manuel Cayoon,2 Patricia Bancalero1 & Alberto Terrión3
1Clinica de Endocrinología, Hospital de las Heras, Granada, Spain; 2Unidad de Diabetes y Medicina del Adulto, Centro de Salud Castillejón, Granada, Spain; 3Servicio de Endocrinología, Hospital Nuestra Señora de la Candelaria, Santa Cruz de Tenerife, Spain.

Introduction
Although the importance of disorders in glucose metabolism is well recognized in human immunodeficiency virus (HIV) infected patients; the clinical relevance of prediabetes in this population has been little studied. The aims of this observational study were to determine the prevalence of prediabetes in a cohort of HIV-infected patients on long term highly active antiretroviral therapy (HAART) and to assess whether this condition involves the appearance of prediabetes in human immunodeficiency virus-infected patients; the clinical relevance of prediabetes in this population has been little studied. The aims of this observational study were to determine the prevalence of prediabetes in a cohort of HIV-infected patients on long term highly active antiretroviral therapy (HAART) and to assess whether this condition involves the appearance of prediabetes in human immunodeficiency virus-infected patients; the clinical relevance of prediabetes in this population has been little studied. The aims of this observational study were to determine the prevalence of prediabetes in a cohort of HIV-infected patients on long term highly active antiretroviral therapy (HAART) and to assess whether this condition involves the appearance of particular clinical and metabolic features.

Methods/design
One hundred and five HIV-positive individuals (85.7% men, mean age: 46 ± 6.5 years) were enrolled. Prediabetes was defined using established ADA criteria. Data related to HIV infection, HCV co-infection and anthropometric and metabolic parameters were recorded. Fasting plasma glucose (FPG), fasting insulin levels and homeostatic model assessment-insulin resistance (HOMA-IR) were determined.

Results
Prevalence of prediabetes was higher (43.1%) among HCV/HIV as compared to 38.3% among those with HIV alone. When compared to normoglycemic controls, patients with prediabetes had significantly (P < 0.05) higher waist-to-hip-ratio (0.96±0.1 vs 0.91±0.11); higher FPG levels (99.4±4.9 vs 90.4±9.6 mg/dl), higher basal insulin (141.1±11.5 vs 86.5±1.1 μIU/l) and higher HOMA-IR (4.4±0.9 vs 1.9±0.2). HCV/HIV with prediabetes were mostly men (100 vs 61%; P < 0.001) and had significantly (P < 0.001) lower LDLc levels (113.2±27.2 vs 90.9±37.7 mg/dl) and lower total cholesterol (180.41 ± 33.47 vs 213.89± 44.6 mg/dl) as compared to prediabetic HIV group. Although FPG levels and HOMA-IR were higher in prediabetic HCV/HIV patients, the difference was not significantly.

Conclusions
HIV patients on long-term HAART are at risk to develop prediabetes, especially if abdominal obesity is present thus, measurements of HOMA-index and waist-to-hip ratio should be routinely done. The worst lipid profile in prediabetic HIV alone suggests that this parameter deserves special attention in these individuals.

DOI: 10.1530/endoabs.32.P365

P366
Clinical experience of a monogenic diabetes unit during 2008–2012 in the Department of Endocrinology and Nutrition (Málaga, Spain)
Marta Domínguez-López,1 J David Fernández-Arias,1 Inmaculada González-Molero,1 Sergio Valdés,1 Juan Miguel Gómez-Zamora,2 Mercedes Guerrero,2 Natalia Colomo,3 Antonio Oñiste,2 David Palau,4 María Soledad Ruiz de Adana & Federico Sorriguer Escotef Carlos Haya Hospital, Malaga, Spain.

Objectives
MODY diabetes is the most common form of monogenic diabetes, encompassing a heterogeneous group of disorders whose primary defect results from mutations in one of at least seven genes recognized, associated with a primary defect in insulin secretion. It has early onset and autosomal dominant inheritance.

Our objective was to evaluate the results of monogenic diabetes clinic of the Endocrinology and Nutrition Department during 2008–2012.

Methods
After evaluating 103 patients referred to the unit for genotyping, only 75 individuals (from 46 families) were included (34 men and 41 women) using the clinical criteria for the diagnosis of monogenic diabetes as ‘Best practice guidelines for the molecular genetic diagnosis of MODY’ (Ellard S et al. Diabetologia 2008). HNF1A was sequenced in 15 patients (20%), HNF1A/HNF4A in 9 patients (12%), GCK in 38 patients (50.6%), HNF1A/HNF4A/GCK (16%) in 12 patients and HNF1A/HNF4A/GCK/HNF1B in one patient (1.3%).

DNA extraction was performed from peripheral blood by kit Maxwell® 16 DNA Purification Kits® (Promega Corporation). Amplification was performed using 18 pairs of specific primers covering the entire gene GKC and HNF1alfa, and 23 pairs of primers for the gene HNF3A. The amplification were sequenced in both directions of the PCR products using the ABI automated sequencer from Applied Biosystems 3130. Subsequent study of the sequences was performed by applying SeqScape Applied Biosystem v2.0 and check Human Gene Mutation Database.

Results
Mutations were found in 6 patients HNF1A of 3 families (L12F, A174V, R200W) and in 22 patients GCK of 9 families (R191W, G227D, T206M, T209M, R43S, L45P, S43L) and in 3 subject HNF4A (T139I, R331 C) belonging to two families. In 24 patients GCK of 9 families (R191W, G227D, T206M, T209M, R43S, L45P, S43L) and in 3 subject HNF4A (T139I, R331 C) belonging to two families.

Conclusions
The low frequency of mutations suggests the involvement of other genes, not identified in the etiology of MODY, not knowing the influence that could have the presence of genetic variants in other genes related to insulin action about its clinical expression.

DOI: 10.1530/endoabs.32.P366

15th European Congress of Endocrinology 2013
Vol 32
Endocrine Abstracts (2013)
P367
Progression to impaired glucose metabolism in normal glucose tolerant urban population
Natalia Piorowska1, Aleksandra Gilis-Jamszewska2, Beata Piwonska-Solska2, Krystyna Szfraniec2, Dorota Puch1 & Alicja Hubalewska-Dyjeczyk3
1Endocrinology Department, Jagiellonian University, Krakow, Poland; 2Public Health Institute, Jagiellonian University, Krakow, Poland.

Objective
To determine the progression rate to impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and diabetes (DM2) and risk factors of progression to diabetes in normal glucose tolerant (NGT) people during 8 years follow up study using WHO 1999 criteria and new criteria of IFG (IFG 5.6-6.9 mmol/l).

Results
This is an 8 year prospective observation in a randomly selected urban population aged ≥ 40 years living in Krakow, Poland. 1752 persons had NGT based on WHO 1999 criteria. 564 of invited person (209 men and 355 women, aged mean 60.7, s.d. = 9.2) attended the follow-up assessment. Subjects underwent a physical examination including weight/height, waist circumference, biochemical examination including OGTT glucose/insulin and questionnaire examination concerning CVD health history and family history of type 2 diabetes. Multiple logistic regression was used to assess the risk factors of progression to diabetes.

P368
Impact of the insulin pump therapy on quality of life children and adolescents with diabetes mellitus type 1
Nikolaeva Nataliya, Bolotova Nina, Kompaniets Olga & Filina Nataliya
Saratov State Medical University, Saratov, Russia.

Objectives
To investigate the changes parameters of quality of life (QoL) in children and adolescents with diabetes mellitus type 1 (T1DM), using different regimes insulin therapy.

Research design and methods
Thirty patients with diabetes mellitus type 1, aged 5–18 years (mean 13.3 ± 3.04 years), with disease duration from 1 to 10 years (mean 5.4 ± 3.4 years) took part in this study. QoL was assessed with the PedsQL (Generic Core Scales and Diabetes Module, Russian version) at two time points: 1st — during multiple daily insulin injection (MDI); 2nd — after initiation continuous subcutaneous insulin infusion (CSII). Data were analyzed in subgroups aged 5–7, 8–12, and 13–18 years.

Results
Nevertheless, analysis demonstrated positive dynamic of QoL in patients after initiation CSII. Treatment barriers decreased due to reduction of a number of injection (75.3 vs 90.0, P < 0.05) in preschool-age children. Patients at the age of 8–12 evaluated higher physical function (74.2 vs 94.0, P < 0.05) after initiation CSII. In adolescent’s group social activity indicates improved (85.0 vs 95.0, P < 0.05). Further, they were less worried about long-term complications (70.0 vs 85.0, P < 0.05).

Conclusions
Using of insulin pump therapy in children with T1DM allows to improve of quality of life. Preschoolers get used to the necessary of insulin therapy easier, schoolchildren and adolescents have opportunity to increase the level of their physical and social activity.

DOI: 10.1530/endobs.32.P368

P369
Relation of serum chemerin level with markers of atherosclerosis in diabetes and prediabetes
Kadiyre Aydin1, Ugur Canpolat2, Muhammet Dural1, Safak Akin1, Jale Karakaya1, Kadret Aytemir1 & Alper Gokalı1
1Department of Endocrinology and Metabolism, Hacettepe University School of Medicine, Ankara, Turkey; 2Department of Cardiology, Hacettepe University School of Medicine, Ankara, Turkey; 3Department of Biostatistics, Hacettepe University School of Medicine, Ankara, Turkey.

Introduction
Chemerin is a novel adipokine that is correlated with adipocyte differentiation, glucose metabolism and inflammation, but its role remains to be elucidated in atherosclerosis particularly in diabetes and prediabetes. We aimed to investigate the relation of serum chemerin levels with markers of atherosclerosis as exemplified by pulse wave velocity (PWV), carotid intima media thickness (CIMT), and carotid plaque presence in these groups.

Methods and materials
We included age, BMI, and gender matched 30 patients with type 2 DM, 19 patients with prediabetes, and 25 healthy individuals with normal glucose tolerance. Serum chemerin levels, lipid parameters, fasting glucose and insulin levels, homeostasis model assessment of insulin resistance (HOMA-IR) were assessed. PWV, CIMT, anthropometric measures, body fat percent, and epicardial fat thickness were recorded.

Results
Serum chemerin levels were similar among groups (226.5 ± 36.8 ng/ml in controls, 242.5 ± 42.8 in prediabetes, 233.0 ± 40.4 in diabetes, P = 0.338), though glucose metabolism parameters including HOMA-IR were higher in patients with type 2 DM. PWV was higher in diabetes than in prediabetes and controls (P = 0.039). Chemerin levels were positively correlated with BMI (r = 0.001, r = 0.425), total cholesterol (r = 0.042, r = 0.239), triglyceride (r = 0.038, r = 0.204), body fat percent (r = 0.007, r = 0.313) and left CIMT (r = 0.032, r = 0.249) in whole group. BMI and body fat percent were also were correlated with chemerin in diabetic group whereas body fat percent and left CIMT remained to be correlated with chemerin in prediabetic group. Eleven patients in the diabetic group, two patients in the prediabetic group and three individuals in the control group had carotid plaque. Chemerin levels were comparable in patients with diabetes when grouped according to the presence of carotids plaque.

Conclusions
Although chemerin is not correlated with atherosclerosis markers as measured by PWV and carotid plaque in diabetes and prediabetes, positive correlation with body fat percent in total group and positive correlation of CIMT and chemerin in prediabetes still arise an unanswered question about its role in atherosclerosis requiring further investigations.

DOI: 10.1530/endobs.32.P369

P370
Serum vaspin levels in women with and without gestational diabetes mellitus during pregnancy and postpartum
Athina Gkiomissi1, Kali Makedour2, Athanasios Anastasilakis3, Stergios Polyzos4, Anargyros Kourtis5, Spyridon Geros5, Elpida Gavana5, Themistoklis Dagklis2, David Roussos2 & Charalambos Giannoullis6
1Clinic of Obstetrics and Gynaecology, 424 Military Hospital, Thessaloniki, Greece; 23rd Department of Obstetrics and Gynaecology, Aristotle University of Thessaloniki, Thessaloniki, Greece; 3Department of Endocrinology, 424 Military Hospital, Thessaloniki, Greece; 2nd Department of Internal Medicine, Aristotle University of Thessaloniki, Ippokration General Hospital, Thessaloniki, Greece; 4Laboratories of Analysis, Thessaloniki, Greece; 52nd Department of Obstetrics and Gynaecology, Aristotle University of Thessaloniki, Thessaloniki, Greece.

Although vaspin is regarded an insulin-sensitizing adipokine, its role in gestational diabetes mellitus (GDM) is currently unknown. We aimed to evaluate serum vaspin levels and their correlation with insulin resistance in women with and without GDM. Forty-four women with GDM Group 20 managed with diet only (GDM-diet) and 24 with diet plus insulin (GDM-insulin) and 44 age-matched pregnant women with normal glucose tolerance (control group) were studied. Serum glucose, lipids, uric acid, insulin, and vaspin were measured at the 2nd and 3rd trimesters of pregnancy and postpartum. The quantitative insulin sensitivity check index (QUICKI) and homeostasis model assessment-insulin resistance (HOMA-IR) were calculated. Circulating vaspin levels decreased significantly postpartum in all groups (P < 0.001), but did not differ between GDM or GDM subgroups and control group in any time point. At the 3rd trimester
of pregnancy vaspin was positively correlated to insulin (P=0.02), HOMA-IR (P=0.016) and triglycerides (P=0.033) and negatively correlated to QUICKI (P=0.016) in the GDM women, but not in the Controls. These correlations could not independently predict GDM in binary logistic regression. In patients with GDM, insulin treatment did not affect vaspin levels. In conclusion, our data suggest that vaspin levels gradually decrease from the 2nd trimester to postpartum; however, decreases are similar between women with or without GDM. Serum vaspin cannot independently predict GDM and it is not affected by the degree of glucose metabolism deregulation or the exogenous administration of insulin.

DOI: 10.1530/endoabs.32.P370

P371

Abstract withdrawn.

DOI: 10.1530/endoabs.32.P371

P372

Association between toll-like receptor 4 polymorphism and type 2 diabetes mellitus

Banu Mesčić1, Pinar Eren2, Safak Kiziltas3, Aytekin Oğuz4, Ilyas Tuncer1, Osman Kostek1 & Yasar Colak1

1Internal Medicine Department, Goztepe Training and Research Hospital, Istanbul Medeniyet University, Istanbul, Turkey; 2Genetic Department, Haydarpaşa Numune Education and Research Hospital, Istanbul, Turkey.

Introduction

Type two diabetes (T2DM), is the most common form of diabetes and known to be associated with low-grade inflammation. Since TLR-4 plays an important role in bacterial recognition of lipopolysaccharide (LPS) and activation of proinflammatory pathways we aimed of to test whether TLR-4 gene polymorphism plays a protective role in the development of T2DM in a pilot Turkish population.

Description of methods/design

Blood samples were collected from 58 patients with T2DM and 63 healthy people. Allelic variants of TLR-4 (Asp299Gly and Thr399Ile) were assayed by real-time PCR. Genomic DNA was amplified using FAM/VIC primers specific for allelic variants of TLR-4 Asp299Gly (rs986790) and Thr399Ile (rs986791) with real-time PCR. Amplons were analyzed with high resolution melting at Light Cycler 480 for detecting different melting patterns of polymorphic and wild type alleles.

Results and conclusion

For genotype 299 gen polymorphism; 17.2% of the patients (n=10) with T2DM were heterozygotic (Asp299Gly), 6.8% (n=4) of them were homozygotic (Gly299Gly) mutant. 9.5% (n=6) of the controls were heterozygotic and 6.3% (n=4) of them were homozygotic. Heterozygotic and homozygotic mutation between patients with T2DM and controls were similar (P=0.21, P=0.9 respectively) For genotype 399 gen polymorphism; 8.6% of the patients (n=5) with T2DM and 9.5% (n=4) of the controls were heterozygotic (Thr299Ile). None of them were homozygotic (Ile299Ile) mutant. Heterozygotic mutation between patients with T2DM and controls were similar (P=0.63). The cumulative mutations number of the subjects with TLR-4 gene polymorphism were similar in groups (17 vs 12, P=0.18). Our results demonstrated that TLR-4 gene polymorphism has no association with T2DM.

DOI: 10.1530/endoabs.32.P372

P373

Altered reactivity of pituitary–adrenal axis to stimulation tests and altered tissue metabolism of cortisol in long-standing type 1 Diabetes

Katerina Simunková1, Karel Vondra1, Michaela Duskova1, Martin Hill1 & Luboslav Starka1

1Institute of Endocrinology, Prague, Czech Republic; 23rd Medical Department, 1st Faculty of Medicine Charles University, General Faculty Hospital, Prague, Czech Republic.

This work aimed to evaluate pituitary–adrenal axis and tissue metabolism of cortisol in patients with long standing type one diabetes. Fifty patients with diabetes type 1 were investigated; age 38±10 years (mean ±SD), age at diagnosis 25.5±10 years, disease duration 15±8 years, BMI 24.5±2.7 kg/m², HbA1c 7.2±1.2%. Control group consisted of 40 healthy volunteers.

The study was approved by the Ethical Committee. Adrenocortical function had been tested by three different tests – Synacthen test, CRH test, and peripheral metabolism of cortisol had been evaluated by cortisone acetate (25 mg) administration and analysis of cortisol/cortisone ratio.

We evaluated serum ACTH, serum cortisol, serum cortisone during these tests, at the basal level cortisol binding globulin, aldosterone, and metabolic parameters of diabetics. Patients with positivity of adrenal autoantibodies, pituitary autoantibodies, thyroid disorders were excluded from group of these patients.

In 15% of patients we have found a subnormal response ( <500 nmol/l) of the serum cortisol during low-dose Synacthen test, accompanied by significantly decreased stimulated values of aldosterone. Basal serum cortisol, aldosterone has been significantly reduced, while ACTH, cortisol binding globulin did not change. The CRH test displayed the low response in serum cortisol and hyperactivity in ACTH in this group of patients. The course of cortisol after cortisone acetate administration was delayed and significantly different in diabetic patients compared to controls.

Conclusion

At least in a part of patients with type 1 diabetes mellitus a reduced secretion of both cortisol and aldosterone after ACTH stimulation could be observed. In diabetic patients peripheral conversion cortisol-cortisone is disturbed as well. These results may contribute to better understanding to pituitary–adrenal adaptation in diabetes type one.

DOI: 10.1530/endoabs.32.P374

P374

The effects of gestational diabetes on basal metabolic rate in pregnancy

Nilay Ergen1, Şami Sabri Bulgurlu2, Akin Dayan2, Ali Erkan Bozat2, Hulya Parıldar2, Nuray Gебелоглу2, Ozlem Tαrcın3, Asli Dogan Unal1 & Refik DemİrtIç2

1Baskent University Istanbul Hospital, Istanbul, Turkey; 2Haydarpaşa Numune Training and Research Hospital, Istanbul, Turkey.

Introduction

The total energy expenditure in pregnancy is increased largely due to elevated basal metabolic rate (BMR) during pregnancy. The aim of this study is to evaluate the effects of gestational diabetes on basal metabolic rate, body weight and HbA1c, by comparing these parameters in gestational diabetic and healthy pregnant women.

Method

Fifty-eight gestational diabetic women (GDM) and forty healthy non diabetic pregnant who had normal thyroid function and not taking any medication which may possibly alter the metabolic rate, recruited in the study. Mean ages of the study population were 21–42 years. GDM was diagnosed by a 100 g OGTT after 50 g oral glucose challenge test. Basal metabolic rate was measured by oxygen consumption after 8 h overnight fasting, also BMI, fasting blood glucose (FBG) and HbA1c were measured in gestational weeks of 24–32. Due to body weight gain as expected during pregnancy, BMR was divided by BMI to ensure normalization.

Results

The rate of BMR to BMI was found 50.30±10.58 kcal/day in GDM group and 51.98±10.58 kcal/day in non-GDM group. The difference was not statistically significant. FBG and HbA1c were higher in GDM women, but not in the Controls. These correlations were significant. FBG and HbA1c were measured in gestational weeks of 24–32. Due to body weight change. The CRH test displayed the low response in serum cortisol and hyperactivity in ACTH in this group of patients. The course of cortisol after cortisone acetate administration was delayed and significantly different in diabetic patients compared to controls.

Discussion

In our study, the average BMR was not different in GDM women compared to pregnant women who do not have gestational diabetics. These results might be different in the third trimester of pregnancy instead of second trimester.

DOI: 10.1530/endoabs.32.P374

Endocrine Abstracts (2013) Vol 32
P376
Prevalence of achievement of HbA1c, blood pressure, and cholesterol (ABC) Goal in Koreans with diabetes
Seong Hoon Yu1, Joon Goo Kang1, Yoo-Cheol Hwang2, Hong Yup Ahn3 & Cheol-Young Park4
1Division of Endocrinology and Metabolism, Department of Internal Medicine, Hallym University College of Medicine, Seoul, Republic of Korea; 2Division of Endocrinology and Metabolism, Department of Medicine, Kyung Hee University Hospital at Gangdong, Kyung Hee University School of Medicine, Seoul, Republic of Korea; 3Division of Endocrinology and Metabolism, Department of Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea.

Introduction
Diabetes is one of the most challenging health problems in the world. The degree of prevention or control of complications directly affects patients' mortality. Therefore, it is crucial to control the risk factors of diabetes. We investigated the prevalence, treatment, and control of diagnosed diabetes in Korean adults from 1998 to 2010.

Methods
The Korean Ministry of Health and Welfare conducted the Korean National Health and Nutrition Examination Survey (KNHANES) in the years 1998 (I), 2001 (II), 2005 (III), 2007–2009 (IV), and 2010 (V). We estimated the prevalence of diagnosed diabetes in Korean adults and the proportions of well-controlled diabetes, as defined having HbA1c <7.0%, blood pressure <130/80 mmHg, and LDL cholesterol <100 mg/dl.

Results
The prevalence of diagnosed diabetes increased significantly from 3.2% in 1998 to 6.4% in 2010 (P < 0.0001). The prevalence of adults with diagnosed diabetes achieving blood pressure, and LDL cholesterol target levels increased from 23.8% to 54.2% (P < 0.0001), and 25.7% to 47.7% (P < 0.0001) respectively. But the percentage of achieving glycemic goals did not increased significantly from 42.5 to 49.1% (P = 0.3034). Furthermore, there were significant increases in the proportions of individuals achieving all three target levels, from 2.7% in 2005 to 8.7% in 2010 (P < 0.0001).

Conclusion
The prevalence of diagnosed diabetes in Korea increased significantly from 1998 to 2010. The percentages of those achieving all recommendations of controlling risk factors have increased, but are still not satisfactory.

DOI: 10.1530/endobs.32.P376

P377
Nutritional status assessment in patients with cystic fibrosis
Matilde Rubio Almanza, Agustín Ramos Prol, Katherine García Malpartida, María Argente Pia, Beatriz León de Zayas, Soledad Navas de Solís, Vicente Campos Alborg, Silvia Sanchís Martín, Roser Querol Ripoll & Juan Francisco Merino Torres
Hospital Universitario Y Politécnico La Fe, Valencia, Spain.

Introduction
Cystic fibrosis (CF) is a chronic disease at risk of malnutrition. The aim of the study is to assess nutritional status of patients with CF.

Methods
Descriptive study of CF patients referred for a nutritional evaluation. Data collected included lung function, pancreatic and carbohydrate metabolism (according to ADA’s diagnostic criteria), anthropometric and laboratory parameters. Results are shown as mean (SD).

Results
Sixty four patients were studied (56.3% males) with a mean age of 26.8 (7.4) years. 100% of them had respiratory involvement and 93.4% exocrine pancreatic dysfunction. 29.5% underwent lung transplantation with a mean age of 22.4 (1.7) years. 50% of patients were diabetic and 21.9%, prediabetic. 37.5% received systemic treatment with corticosteroids. BMI was 19.2 (2.7) kg/m². The ideal percentage weight was 83.9% (13.3) and weight loss in the last 6 months was 3.6% (5.8). The main causes of weight loss were respiratory infections (55.6%), decreased appetite or early satiety (32.1%), and steatorrhea (14.8%). Vitamin D deficiency was present in 60.9%, vitamin A in 70.6% and vitamin E in 72.5%. Severe malnutrition was diagnosed in 20.4% of patients, moderate in 22.2% and mild in 25.9% of cases. Mixed malnutrition was found in 51.4%. Protein in 29.7% and caloric intake, 9%. Diabetes was associated with vitamin D deficiency <30 ng/ml (P = 0.01) and lung transplantation (P < 0.001). Severe malnutrition is statistically associated with lung transplantation (P = 0.01), systemic corticosteroid therapy (P = 0.01), and diabetes (P = 0.04).

Conclusion
A high prevalence of malnutrition (73%) was found in CF patients. Severe malnutrition was associated with lung transplantation, systemic corticosteroid therapy, and diabetes. Posttransplant assessment of nutritional status is important in CF patients. Diabetes was associated with lung transplantation and vitamin D deficiency.

DOI: 10.1530/endobs.32.P377

P378
The expression mechanism of lipocalin-2 by co-stimulation with interferon γ in RINm5F β-cells
Seo-Yoon Chang1, Dong-Bin Kim1,2, Yang-Hyeok Jo1 & Myung-Jun Kim1
1Department of Physiology, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; 2Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea.

Lipocalin-2 (LCN-2) is known to act as an antiinflammatory or a proinflammatory mediator. Recently, LCN-2 has been recognized to play a role in obesity and insulin resistance. However, there is no knowledge about the expression and the role of LCN-2 in pancreatic islet β-cells. Therefore, we examined molecular mechanisms by which proinflammatory cytokines interleukin 1β (IL1β) and interferon γ (IFNγ) induce LCN-2 expression in RINm5F β-cells. IL1β significantly induced LCN-2 protein and mRNA expression. IFNγ alone did not induce LCN-2 protein and mRNA expression whereas IFNγ significantly stimulated IL1β-induced LCN-2 expression. However, promoter study and EMSA showed that IFNγ failed to stimulate IL1β-induced LCN-2 promoter activity and binding activity of NFκB on LCN-2 promoter. Meanwhile, western blot using NFκB inhibitor and promoter assay using truncated constructs showed that NFκB was a key factor in IL1β-induced LCN-2 expression. However, NFκB and STAT-1 were not involved in stimulatory effect of IFNγ on IL1β-induced LCN-2 expression. Furthermore, we found that LCN-2 expression was significantly increased and prolonged compared with both INS and COX-2 expression under exposure to IL1β, and that LCN-2 receptor was expressed in pancreatic β-cells. Our data suggest that IL1β induced LCN-2 expression via NFκB activation and IFNγ significantly stimulated IL1β-induced LCN-2 expression at protein and mRNA level but not at promoter activity. This effect of IFNγ was not independent of NFκB and STAT-1 activation. In addition, abundant expression of LCN-2 and LCN-2 receptor in β-cells implies that LCN-2 plays a role in β-cell function. Our data suggest that IFNγ significantly potentiates IL1β-induced LCN-2 expression at mRNA and protein level but not at promoter level, and NFκB plays a key role in IL1β-induced LCN-2 expression. In...
addition, abundant expression of LCN-2 and LCN-2 receptor in β-cells implies that LCN-2 plays a role in β-cell function.

DOI: 10.1530/endoabs.32.P378

P379

The effect of CCR2 G190A gene polymorphism on development of diabetic coronary artery disease
Gökhan Bagci1,2, Binnur Koksal1, & Beda Cakmakoglu3
1Cumhuriyet University Medical Genetics, Sivas, Turkey; 2Bartin University Molecular Biology and Genetics, Bartin, Turkey; 3Istanbul University Molecular Medicine, Istanbul, Turkey.

Introduction
Inflammatory mechanisms play an important role in the development of cardiovascular diseases and diabetes. Chemokines are chemotactic cytokines that orchestrate leukocyte trafficking in tissues, thus, playing an important role in regulation of immunological processes. Some studies have shown that CCR2 G190A polymorphism might be important for protection of susceptibility to some immunologically-mediated disorders. The aim of our study was to investigate the effect of the CCR2 G190A polymorphism on the development of diabetic coronary heart disease.

Methods
Sixty two diabetic patient with coronary heart disease, 81 diabetic patient without coronary heart disease, and 62 disease-free 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. The CCR2 G190A genotype was determined by PCR followed by RFLP.

Results
No significant difference in the frequency of the CCR2 polymorphism between patient groups and the controls was found ($P=0.78 \times 0.48$).

Conclusion
In contrast, we did not find any significant difference in CCR2 G190A polymorphism in diabetic patients with coronary heart disease, diabetic patient without coronary heart disease and healthy controls.

DOI: 10.1530/endoabs.32.P379

P380

High prevalence of the metabolic syndrome among newly diagnosed type 2 diabetes patients in Denmark
Jens Steen Nielsen1, Reimar W Thomsen2, Sinna Pilgaard Ulrichsen2, Anil Most1, Jacob Volmer Stidsen1, Jørgen Rungby1, Søren Fribern1, Ivan Brandts1, Jens Sandahl Christensen1, Henrik Toft Sorensen2 & Henning Beck-Nielsen1
1Department of Endocrinology, Diabetes Research Centre, Odense University Hospital, Odense, Denmark; 2Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; 3Department of Pharmacology, University of Aarhus, Aarhus, Denmark; 4Department of Biochemistry, Lillebaelt Hospital Vejle, Vejle, Denmark; 5Department of Internal Medicine and Endocrinology, Aarhus University Hospital, Aarhus, Denmark.

Few population-based data exist on the prevalence of the metabolic syndrome (MS) its components, and its association with subclinical inflammation and insulin resistance among patients newly diagnosed with type two diabetes (T2D). We examined the MS according to IDF criteria by linkage primary data (waist circumference, fasting blood glucose, and high-sensitivity C-reactive protein (CRP)) with variables from the Danish diabetes database for adults (blood pressure and lipids) and a nationwide prescription database (antilipidemic, fibrinogen, total cholesterol, triglycerides, ischemic cardiomyopathy by EKG, and the presence of LVH by echocardiography). Cardiovascular, infectious and metabolic complications during or after elective surgery were registered till the time of discharge. Patients with cetonuria, hypoglycemia or clinical conditions that could interfere with the diagnosis of persistent microalbuminuria and autonomic neuropathy were excluded. Significant associations were determined through chi square tests and linear regression analyses.

Results
Sixty two patients were evaluated (mean age: 60.5 years, 20–80 years range; 69.6% females). The most frequent complications were hypertension ($n=21$), hyperglycemia ($n=24$) and surgical wound infection ($n=20$). Analysis identified a significant association between age ($P=0.04$; OR: 4.98, s.e.m.: 0.73 ($B=1.60, P=0.02$)), Hb1Ac ≥7% ($P=0.01$; OR: 12.77, s.e.m.: 0.92 ($B=2.54, P=0.006$)), EKG with ischemic cardiomyopathy ($P=0.04$; OR: 4.14, s.e.m.: 0.82 ($B=1.42, P=0.08$)) and general anesthesia ($P=0.03$; OR: 10.63, s.e.m.: 0.83 ($B=2.36, P=0.004$)) with more cardiovascular complications during or after surgery; glucose ≥126 mg/dl ($P=0.04$; OR: 3.62, s.e.m.: 0.74 ($B=1.28, P=0.08$)) and Hb1Ac ≥7% ($P=0.01$; OR: 6.43, s.e.m.: 0.81 ($B=1.84, P=0.02$)) were associated with more metabolic complications during or after surgery; No other parameter measured was significantly associated with cardiovascular, infectious or metabolic complication during or after elective surgery.

Conclusions
Significant association were found between age, Hb1Ac levels, type of anesthesia and EKG with evidence of ischemic cardiomyopathy and cardiovascular complications; preoperative glycaemia and Hb1Ac were associated with metabolic complications. The evaluation of the metabolic status of T2DM patients before elective surgery may help to anticipate trans- or post-operative complications.

DOI: 10.1530/endoabs.32.P380

P381

Trans-operative and post-operative medical complications in patients with diabetes mellitus type 2
Atil Abreu & Johann Diaz
Centro Medico Imbanaco, Cali, Valle del Cauca, Colombia.

Purpose
To determine the association between clinical indicators of metabolic state and cardiovascular, infectious and metabolic complications during or after elective surgery in patients with type 2 diabetes mellitus (T2DM) regardless of their treatment scheme.

Methods
Prospective observational study. Patients with T2DM, ages 20–80 years, scheduled for elective surgery were evaluated with office BP, BMI, Hb1Ac, fasting glucose, fibrinogen, total cholesterol, triglycerides, ischemic cardiomyopathy by EKG, and the presence of LVH by echocardiography. Cardiovascular, infectious and metabolic complications during or after elective surgery were registered till the time of discharge. Patients with cetonuria, hypoglycemia or clinical conditions that could interfere with the diagnosis of persistent microalbuminuria and autonomic neuropathy were excluded. Significant associations were determined through chi square tests and linear regression analyses.

Results
Sixty two patients were evaluated (mean age: 60.5 years, 20–80 years range; 69.6% females). The most frequent complications were hypertension ($n=21$), hyperglycemia ($n=24$) and surgical wound infection ($n=20$). Analysis identified a significant association between age ($P=0.04$; OR: 4.98, s.e.m.: 0.73 ($B=1.60, P=0.02$)), Hb1Ac ≥7% ($P=0.01$; OR: 12.77, s.e.m.: 0.92 ($B=2.54, P=0.006$)), EKG with ischemic cardiomyopathy ($P=0.04$; OR: 4.14, s.e.m.: 0.82 ($B=1.42, P=0.08$)) and general anesthesia ($P=0.03$; OR: 10.63, s.e.m.: 0.83 ($B=2.36, P=0.004$)) with more cardiovascular complications during or after surgery; glucose ≥126 mg/dl ($P=0.04$; OR: 3.62, s.e.m.: 0.74 ($B=1.28, P=0.08$)) and Hb1Ac ≥7% ($P=0.01$; OR: 6.43, s.e.m.: 0.81 ($B=1.84, P=0.02$)) were associated with more metabolic complications during or after surgery; No other parameter measured was significantly associated with cardiovascular, infectious or metabolic complication during or after elective surgery.

Conclusions
Significant association were found between age, Hb1Ac levels, type of anesthesia and EKG with evidence of ischemic cardiomyopathy and cardiovascular complications; preoperative glycaemia and Hb1Ac were associated with metabolic complications. The evaluation of the metabolic status of T2DM patients before elective surgery may help to anticipate trans- or post-operative complications.

DOI: 10.1530/endoabs.32.P381

P382

Assessment of pre-pregnancy BMI in patients with gestational diabetes
Amapuro Segura-Galindo, Ana María Fernández-Alonso, Immaculada Moreno-Ruiz, Virginia Sebastián-Ibáñez & Francisco Javier del Cañizo-Gómez
Hospital Universitario Infanta Leonor, Madrid, Spain.

Objectives
Relationship between pre-pregnancy BMI (PPBMI) in gestational diabetic (GD) patients, and age, country of origin, family history of type 2 diabetes mellitus (T2DM), GD history, and BMI after pregnancy.

Methods
Transversal, descriptive study of 250 consecutive pregnant with confirmed DG. Analysis were based on Fisher’s exact test and Student’s t-test. A $P<0.05$ was significant (SPSS 19.0).

Endocrine Abstracts (2013) Vol 32
Results
Mean age was 34.3 years, 49.8% primiparous, 66.7% Spanish, 17.4% South American, 5.5% Eastern European, 3.1% North African, 2.0% South Africans, 3.5% Chinese, 0.8% Indian, and 0.4% Portuguese/Cuban. Women with a family history of T2DM had a mean average of 2.51 kg/m² PPBMI higher than pregnant women without such a history (P < 0.001). The mean PPBMI was 27.1 kg/m² (30% overweight and 28.0% obese). Thirty-three percent of Spanish pregnant were overweight and 25.4% obese, vs 22.6 and 33.3% respectively amongst the other countries. A positive correlation was observed between age and PPBMI (P = 0.012). There was a statistically significant difference for the PPBMI of the primiparous compared to the multiparous, with a mean difference of 2.4 kg/m² in favour of the latter. Postpartum mean BMI between 4 and 6 months after delivery was 27.2 kg/m² showing no significant difference to the PPBMI.

Conclusions
Is interesting the high average age of the pregnant, the high percentage of overweight and obese women before pregnancy and the positive correlation of PPBMI and age in all pregnant. However PPBMI is higher in multiparous and was positively correlated with family history of T2DM. The data observed in the study population suggest the possibility of an increase in the development of T2DM in these patients, so it will be advisable to tighter control of the same.

DOI: 10.1530/endoaabs.32.P382

P383
Study of the development and validation of the specific “Satiglu” questionnaire to evaluate the satisfaction of diabetic patients with glucometers
Cristobal Morales Portillo1, Clara Garcia Garcia1, Florentino Carral Sanlaureano2, Juan Carlos Huerga3, Martin Lopez de la Torre Casares3 & Javier Hurtado4
1Hospital Virgen Macarena, Seville, Spain; 2Hospital Puerto Real, Cadiz, Spain; 3Hospital Osuna, Seville, Spain; 4Hospital Virgen de las Nieves, Granada, Spain.

Objective
To develop a specific questionnaire to evaluate the satisfaction of diabetic patients with the use of glucometers and evaluate their psychometric properties (feasibility, reliability, and validity).

Material and methods
Two stages: i) questionnaire development: a set of 53 items was constructed after a bibliographic review. A panel of six experts and 50 patients concluded a 25 item version of the questionnaire (dimensions: satisfaction, inconvenience, added value, and appearance). ii) Questionnaire validation: 6-month, epide-miological, multcentre, cross-sectional study that recruited 286 adult patients with type 1 or 2 diabetes mellitus (DM) who used a glucometer. Their responses to the questionnaire were collected together with supplementary variables: sociodemographic and clinical, adherence to treatment (Morsisky-Green), generic satisfaction with treatment questionnaire, SAT-Q, and also specifically for diabetes, DTQ5-s. The questionnaire’s test-retest reliability was evaluated by 51 patients completing the questionnaire 15 days after the visit.

Results
The mean age (SD) of the sample was 42.70 years (16.25), 55.30% were women and 63.70% presented type I DM. The patients’ mean percentage (S.D.) of HbA1c was 7.82% (1.45). Mean adherence was 7.65 (1.66), the patients had been using a glucometer for a mean time of 6 years, and average glycaemia controls were 3.95 (1.76). 73.50% of the patients had obtained the glucometer from an institution for a mean time of 6 years, and average glycaemia controls were 3.95 (1.76). Females (62%) vs 32/60 (53%) males in control group). Severity of vitamin D deficiency (<10 ng/ml) was higher in cases (48.2%) than controls (26.2%). IL6 was higher in cases (128.3 pg/ml) than the controls (63.8 pg/ml) (P = 0.01). Similarly lower median plasma levels of adiponectin (7.7 vs 8.4 µg/ml) and higher median plasma levels of resistin (3.8 vs 3.6 ng/ml) were observed in cases (P<0.05). No significant difference was observed in the levels of these markers between male and female study participants in both the groups. Patients under vitamin D deficient group (<30 ng/ml) demonstrated higher IL6 (130.8 vs 100.0 pg/ml), higher resistin (3.9 vs 3.6 ng/ml) and lower adiponectin (7.6 vs 8.3 µg/ml) levels compared to vitamin D sufficient (≥30 ng/ml) group in diabetic foot (P<0.05).

Discussion
Immuno-regulatory role of vitamin D is well established. Diabetic foot infections reflect the immune-compromised state of the patients and therefore it is stipulated that vitamin D deficiency is more common and severe in diabetic foot. Our study demonstrated that diabetic subjects with diabetic foot showed in comparison with diabetics without diabetic foot higher IL6 and resistin plasma levels and lower adiponectin plasma levels. Hypovitaminosis D is more prevalent in patients with diabetic foot and vitamin D deficiency is more severe in patients with diabetic foot infections. The levels of the above markers are more in diabetic foot patients with vitamin D deficiency.

Conclusions
Assumption is made that vitamin D deficiency enhances inflammatory response in addition to hyperglycaemia, in diabetic foot.

DOI: 10.1530/endoaabs.32.P384

P385
Study of the prevalence of subclinical hypothyroidism in type 2 diabetic Egyptian women
Hussein Eloraby, Mohammed Halawa, Mona Abdelsalam, Rania Abdelbaki & Bassim Moustafa
Endocrinology and Metabolism Unit, Internal Medicine Department, Ain Shams University, Cairo, Egypt.

Background
Subclinical hypothyroidism is a common thyroid disorder. Although there is a recognized association between thyroid disease and diabetes mellitus, there is no definite answer as to whether screening for subclinical hypothyroidism is necessary in patients with type 2 diabetes.

Objective
To evaluate the prevalence of subclinical hypothyroidism in women with type 2 diabetes in Egypt.

Patients and methods
women with type 2 diabetes (54.3 ± 9.3 years) and 100 women without diabetes (49.2 ± 5.3 years) participated. Those with type 1 diabetes, thyroid disorders, chronic illness or receiving drugs that affect thyroid function were excluded. They were assessed for TSH, HbA1c, lipid profile, ultrasound, CRP, urine...
albumin:creatinine ratio and thyroid parameters as TSH, FT₄, anti-thyroid peroxidase antibodies (TPO), and thyroid volume by neck ultrasound.

Results
The prevalence of subclinical hypothyroidism was 9% in diabetic patients and 3% in control subjects with no significant statistical difference between the two groups (P=0.09). FT₄ was lower in diabetic group than controls with P<0.001. TSH was higher in diabetics than control with P<0.01. The prevalence of TPO was similar in both groups (P=0.3) as well as the thyroid volume (P=0.8).

Across all participants, positivity for TPO was significantly higher in patients with subclinical hypothyroidism than in euthyroid subjects. usCRP was higher in diabetic patients (P<0.001), and was positively correlated with parameters of the metabolic profile rather than the thyroid profile parameters. In our study, thyroid parameters among different stages of diabetic nephropathy showed no significant difference, but patients with macroalbuminuria have the lowest FT₄ values and highest TSH values.

Conclusion
The statistical insignificant difference in the prevalence of subclinical hypothyroidism in women with type 2 diabetes and women without diabetes suggests that routine screening of thyroid function in patients with type 2 diabetes is unwarranted. However, further mega studies are recommended.

DOI: 10.1530/endoabs.32.P385

P386
Maternal serum fetuin-A, lepint, and hs-CRP concentrations in gestational diabetes
Mehmet Calan¹, Ozgur Yilmaz², Tamer Akindag³, Ahmet Solak⁴, Levent Kebabci², Huseyin Oguz Yuvarc⁵ & Tuba Dal⁶
¹Department of Obstetrics and Gynecology, Manisa Akhisar State Hospital, Manisa, Turkey; ²Division of Endocrinology and Metabolism, Department of Internal Medicine, Dokuz Eylul University, Izmir, Turkey; ³Department of Obstetrics and Gynecology, Bursa Acibadem Hospital, Bursa, Turkey; ⁴Department of Biochemistry, Van Ipekolu Hospital, Van, Turkey; ⁵Division of Endocrinology and Metabolism, Department of Internal Medicine, Sulecul, Medical Faculty, Konya, Turkey; ⁶Department of Obstetrics and Gynecology, Diyarbakir, Turkey.

Aim
The aim of this study was to examine serum fetuin-A, lepint, and hs-CRP concentrations among pregnant women with gestational diabetes (GDM), and to evaluate the relationship between these parameters and insulin resistance.

Materials and methods
In this study, we evaluated 47 pregnant patients with GDM. As the control group, 43 normal pregnant women having similar properties with these GDM patients, but not gestational diabetes were enrolled. Serum fetuin-A, lepint, and high sensitive CRP (serum reactive protein) levels of both groups of pregnant women were measured. Insulin sensitivity and insulin resistance were calculated by QUICKI-İS (quantitative insulin check index) and HOMA-İR (homeostasis model assessment of insulin resistance) methods respectively.

Results
Fasting serum glucose levels (P<0.001), fasting serum insulin levels (P=0.002), HOMA-İR index (P=0.001), serum leptin levels (P=0.002), and serum hs-CRP levels (P<0.001) of the women with GDM were found statistically significantly higher than the control group. Serum fetuin-A levels and HOMA-İR index showed no statistically significant difference between the two groups.

Conclusion
Pregnant women with and without GDM were compared in terms of serum fetuin-A levels and no statistically significant difference was detected between the two groups. In addition, insulin resistance calculated by HOMA-İR and fetuin-A showed no significant correlation between the two groups of patients. Serum leptin and hs-CRP concentrations increased in women with GDM, and a significant positive correlation was found between serum leptin hs-CRP and insulin resistance.

DOI: 10.1530/endoabs.32.P386

P388
Identification of plasma biomarkers in human diabetic retinopathy
Ying-Ray Lee¹, Chieh-Hsiang Lu² & Hong-Lin Chan³
¹Department of Medical Research, Chiayi Christian Hospital, Chiayi, Taiwan; ²Division of Endocrinology and Metabolism, Department of Internal Medicine, Chiayi Christian Hospital, Chiayi, Taiwan; ³Department of Medical Science, Institute of Bioinformatics and Structural Biology, National Tsing Hua University, Hsinchu, Taiwan.

Retinopathy has been observed in around 25% of patients with type one and type two diabetes for 3–5 years. Diabetic retinopathy can cause poor vision and even blindness since high glucose has been evidenced to weaken retinal capillary leading to leakage of blood into the surrounding space. Therefore, the prevention, diagnosis and therapy of diabetes retinopathy are very important in diabetes patients. Here, we adopted a proteomics-based approach using 2D-DIGE and MALDI-TOF/TOF MS to compare the differential plasma proteome between patients. Here, we adopted a proteomics-based approach using 2D-DIGE and MALDI-TOF/TOF MS to compare the differential plasma proteome between diabetic retinopathy with significant retinopathy occurrence within 5 years after diagnosis of diabetes, and diabetic non-retinopathy without diagnosed retinopathy for more than 10 years after diagnosis of diabetes. In this study, we identified proteins differential expression in the plasma of diabetic retinopathy patients. These proteins mainly have inflammatory response and coagulation roles, and may be associated with the progression and development of diabetes. In conclusion, we report a comprehensive patient-based plasma proteomic approach to the identification of potential plasma biomarkers for diabetic retinopathy screening and detection.

DOI: 10.1530/endoabs.32.P388

P387
The impact of fasting during Ramadan on the glycemic control of patients with type 2 diabetes mellitus
Serap Baydar Sahin¹, Teseime Ayaz², Neslihan Ozyurt², Kadir Ikiklic³, Abdulkadir Kirvari¹ & Hacer Sezgin³
¹Department of Endocrinology and Metabolism Disease, Recep Tayyip Erdogan University Medical School, Rize, Turkey; ²Department of Internal Medicine, Recep Tayyip Erdogan University Medical School, Rize, Turkey.

Background
Millions of Muslims fast from dawn until dusk during the annual Islamic holy month of Ramadan. Most of the studies evaluating biochemical changes in diabetic patients during Ramadan showed little changes in the glycemic control. In this study, our aim was to assess the impact of fasting during Ramadan on glycemic control in patients with type 2 diabetes.

Methods and design
We examined 122 patients with type 2 diabetes (82 females, 40 males, age 56.93±9.57 years) before and after the Ramadan. 66.4% of the patients were treated with oral antidiabetic (OAD) alone, 7.4% with a combination of OAD plus exenatide, 6.5% with a combination of insulin plus OAD and 19.7% with insulin alone. 88 of 122 patients fasted during Ramadan (26.98±5.93 days). Weight, BMI, waist circumference, blood pressure, fasting plasma glucose (FPG), postprandial glucose (PPG), fructosamine, HbA1c, fasting insulin, and lipid parameters were measured.

Results
The frequencies of both severe hypoglycemia and hyperglycemia were higher in the fasting group, but the difference was not significant (P=0.18). Weight (89.86±17.20 vs 89.22±16.68 kg, P=0.069), BMI (36.32±15.33 vs 35.71±11.47 kg/m², P=0.30), waist circumference (106.97±15.57 vs 106.06±14.04 cm, P=0.535), blood pressure, FPG (143.38±52.04 vs 139.31±43.47 mg/dl, P=0.758), PPG (213.40±98.56 vs 215.66±109.31 mg/dl, P=0.634), fructosamine (314.18±75.40 vs 314.49±68.56 µmol/l, P=0.114), HbA1c (6.33±0.98 vs 6.22±0.92%, P=0.057), fasting insulin (12.61±6.84 vs 10.51±6.26 µU/ml, P=0.200) and lipid parameters were unchanged in patients who fasted during Ramadan.

Conclusions
In this study, we concluded that fasting during Ramadan did not worsen the glycemic control of patients with type 2 diabetes.

DOI: 10.1530/endoabs.32.P387
P389
Diabetes awareness in the general population of northern Greece
Maria Somalī1, Christos Darianis2, Georgios Mastorakos3 & Zadalla Mouslech1
1National Organization for Health Care (ΕΟΠΥΥ), Thessaloniki, Greece; 2Department of Biology, Faculty of Sciences, Aristotle University, Thessaloniki, Greece; 3Department of Endocrinology, Metabolism and Diabetes, School of Medicine, Aretaedio Hospital, National and Kapodistrian University of Athens, Athens, Greece.

Introduction
The current study was conducted to assess the level of awareness about diabetes in a random population.

Methods
A questionnaire was conducted by communication over the telephone in Thessaloniki, Macedonia, and Greece in a random population of 600 persons. Presence of DM1 or DM2 in the person questioned or a family member, knowledge of precipitating factors, duration, curability, choice of physician and compliance with medication were assessed.

Results
In the total population, 14% had diabetes. 41% reported their first choice of physician would be an endocrinologist, 36% an internist, 5% a general physician and 18% (DKn/NA). Among those with diabetes, 64% reported total compliance with doctors’ recommendations, 5% high, 15% mostly, 8% little, and 5% no compliance. 28% of the population free of diabetes reported a family member with diabetes, 94% of these reported no concealment of the disease in their social behavior.

Conclusion
We believe that the level of awareness of diabetes in northern Greece is satisfactory. Communication to the general population of the main predisposing factors especially obesity and the importance of compliance to treatment in order to optimize treatment and avoid complications are needed.

DOI: 10.1530/endoabs.32.P389

P390
Insulin resistance among adults with type 1 diabetes mellitus
Jerome Barrera, Cecilia Jimeno & Elizabeth Paz-Pacheco
Philippine General Hospital, Manila, Metro Manila, The Philippines.

Insulin resistance (IR) has been proven to increase the risks for cardiovascular complications in type 2 diabetes mellitus. Recently, IR has also been shown to play a bigger role in the natural history of type 1 diabetes mellitus (T1DM) disease process than is commonly recognized. The objectives of this study are to determine the prevalence of IR among Filipino adults with T1DM and to describe the clinical features of T1DM with IR.

This cross-sectional analytic study recruited 83 adults with established T1DM in the Philippine General Hospital. Mixed-meal stimulated C-peptide level was done to confirm the diagnosis of T1DM. IR was determined using estimated glucose disposal rate (eGDR) with the formula of: eGDR = 24.31 (12.22 x waist-to-hip ratio) – 3.29 x 1 if with hypertension or on anti-hypertensive or × 0 if no hypertension – (0.57 x HbA1c). Subjects with eGDR of ≤ 7.5 mg/kg per min were considered to have IR.

The prevalence rate of IR was found to be 53%. T1DM subjects with IR were significantly older (29.59 vs 25.59, P=0.007), with longer duration of diabetes (59.7 vs 40.3% with duration of diabetes > 5 years, P=0.037), with higher waist-to-hip ratio (0.95 vs 0.93, P=0.005) and with higher rate of hypertension (100 vs 8%, P=0.00) than those without IR.

The study showed a high prevalence rate of IR among Filipino adults with established T1DM. Hypertension, older age, longer duration of disease and a higher waist-to-hip ratio are the features of T1DM with IR.

DOI: 10.1530/endoabs.32.P390

P391
Atypical early onset Werner’s syndrome
Berna Imge Aydogan, Seda Yürümez, Gözde Sengül, Mustafa Sahin & Nilgün Baskal
Department of Endocrinology and Metabolism Diseases, Faculty of Medicine, Ankara University, Ankara, Turkey.

Introduction
Werner’s Syndrome (WS) is a rare autosomal recessive adult onset progeroid disorder characterized by the early onset of aged-appearance and age related metabolic disorders. Patients usually develop normally until the 3rd decades of life.

Case report
We report a 27 years old female who admitted to our clinic at the age of 15 with hyperglycemia. She was diagnosed as diabetes and type 4 dyslipidemia at the age of 7 years. In her family history, her parents were first cousins and she had three healthy brothers.

At her first examination she had bird-like face appearance, short stature and she was overweight. She had global alopexia with gray and thin hair. Her voice was hoarse and hyperkerosis of skin was present at dermatological examination. She had bilateral cataracts and moderate sensorineural hearing loss. At psychiatric examination she had borderline mental retardation.

She has got severe insulin resistance and hypertriglyceridemia despite therapy with insulin, levothyroxine, gemfibrozil and omega-3. Routine lipid apheresis has been performed to lower the triglyceride levels reaching 5256 mg/dl.

She also had focal segmental glomerulosclerosis, hepatosteatosis, osteoporosis and epilepsy. She had several congenital deformities like rathke’s cleft cyst, angiomyolipoma and femoral neck hypoplasia.

Discussion and conclusion
Werner’s syndrome may have very early onset and present with severe hypertriglyceridemia and multiple metabolic and congenital abnormalities.

DOI: 10.1530/endoabs.32.P391

P392
Potentialities of skin impedance spectroscopy in vivo in non-invasive monitoring of glucose level
Turkovskiy Ivan1, Paramonov Boris1, Kharin Vitaly1, Gericke Monica2 & Belyaev Nicolay3
1Ltd. Noninvasive Technology, Saint-Petersburg, Russia; 2GmbH GetiNov, Zurich, Switzerland.

Considered are the physiological mechanisms of relationship of the magnitude of blood plasma and interstitial fluid osmolarity conditioned by glycaemia with transmembrane movement of water between intra- and extracellular water compartments of organism. Analysed are the potentialities of impedance spectroscopy in quantitative evaluation of increments of specific volumes of extra- and intracellular fluid of hypoderm tissues occurring due to fluctuations of intercellular fluid glucose level. Substantiated is the possibility of technical implementation of individual systems for non-invasive monitoring of glucose concentration in intercellular fluid on the base of two-frequencies (30 and 1000 kHz) impedancemetry of human skin. Represented are the results of interstitial liquid glucose level calculation performed on the base of transcutaneous measurement of wrist tissues impedance in persons ill with diabetes 1 and 2 and in healthy volunteers. Fulfilled is the comparative analysis of results of glucose level calculation on the base of impedancemetry with the reference data obtained by invasive measurements in blood and interstitial liquid by system invasive glucose monitoring Medtronic Guardian Real Time. Revealed is the strong correlation – Pearson’s coefficient is higher than 0.8 – between the results of calculated glucose concentration on the base of impedancemetry and reference data obtained by invasive measurements.

DOI: 10.1530/endoabs.32.P392
P393

Association of plasma testosterone concentration with cardiovascular risk factors in young Chinese men of type 2 diabetes mellitus
Xin Li, Miao Yang, Yuwen Wu & SuXin Sun
Department of Endocrinology, Zhongnan Hospital, Wuhan University, Wuhan City, Hubei Province, China.

Introduction
Type 2 diabetes mellitus (T2DM) has the same risk of cardiovascular event with coronary artery disease (CAD). Men with diabetes are characterized by a decrease in circulating testosterone concentrations, and testosterone deficiency have been associated with increased risk of metabolic syndrome and CAD. With the increased popularity of western life style in China, the morbidity of T2DM increased greatly in young Chinese people. This study aimed to investigate the association of plasma testosterone concentration with certain cardiovascular risk factors in young Chinese men of T2DM.

Methods and design
We reviewed 300 aged 18–30 male T2DM patients in the Zhongnan Hospital, Wuhan University through 2010–2011. All the patients were given oral glucose tolerance test (OGTT), insulin release test (IRT), and the detection of serum testosterone, serum lipid, Hs-CRP. All the patients were given electrocardiogram and detection of myocardium enzyme to rule out the acute coronary syndrome.

Results
Serum testosterone was significantly correlated with age ($r = -0.14$), BMI ($r = -0.15$), waist circumference ($r = -0.21$), triglyceride (TG) ($r = -0.23$), Hs-CRP ($r = -0.26$), MHP ($r = -0.12$), and HOMA-IR ($r = -0.24$) (all $P < 0.01$). After adjustment for BMI, waist circumference, age and smoking history, the plasma testosterone was still significantly correlated with Hs-CRP, HOMA-IR, and TG. There were 180 patients with smoking history who had lower serum testosterone concentration in compared with non-smokers in this study, but the difference was not significant. There was no significant difference in the plasma testosterone concentration between the patients with or without coronary heart disease family history. Multiple regression analysis indicated that serum testosterone concentration was the independent predictor of HOMA-IR, Hs-CRP, and TG.

Conclusions
Serum testosterone in young T2DM men was significantly and independently correlated with HOMA-IR, Hs-CRP, and TG, and might be one of the predictors of cardiovascular disease.

DOI: 10.1530/endoabs.32.P393

P395

Leptin, resistin and omentin in patients with the obesity and with impaired glucose tolerance
Andrey Verbovoy & Elena Solomonova
Samara State Medical University, Samara, Russia.

Aim
To evaluate the adipocins content in the blood with IGT.

Materials and methods
One hundred and one patients with IGT were examined (86 women and 15 men) middle-aged 62.1 ± 12 years old. The control group included 16 patients (eight women and eight men) middle-aged 22.6 ± 0.6 years old. The anthropometric indications (IMB, WC, and WC/TC), HOMA-IR, insulin, CRP, resistin, leptin, and omentin levels were investigated.

Results
All patients with IGT had IMB more than 30 kg/m², WC in men was higher than 94 sm, in women – 80 sm, that shows that they have visceral obesity type. HOMA-IR, insulin, CRP levels in patients with IGT is actually higher (4.12 ± 0.28, 16.14 ± 0.93 ng/ml and 4.82 ± 0.63 mg/l accordingly) than in control group (1.48 ± 0.11, 7.78 ± 0.43 ng/ml and 2.67 ± 0.56 mg/l accordingly, $P < 0.001$). Resistin level in IGT was statistically higher (9.85 ± 0.41 ng/ml), than in control group (7.46 ± 0.51 ng/ml, $P < 0.05$). The lower omentin content in the patients blood with IGT (271.52 ± 14.92 ng/ml) compared with the control group (395.6 ± 5.3 ng/ml, $P < 0.001$). The leptin content in the men’s blood (12.2 ± 4.5 ng/ml) and IGT women (40.95 ± 3.04 ng/ml) is actually higher than in control group (3.59 ± 0.38 ng/ml in men and 9.56 ± 0.67 mg/l in women, $P < 0.001$). The leptin level in IGT women positively correlates with IMB ($r = 0.612$, $P < 0.001$). WC ($r = 0.743$, $P < 0.001$), insulin level ($r = 0.519$, $P < 0.01$), HOMA-IR ($r = 0.496$, $P < 0.001$), CRP level ($r = 0.515$, $P < 0.01$), and negatively correlates with omentin level ($r = -0.804$, $P < 0.001$).

Conclusion
The increase of leptin and resistin levels and reduction of omentin level are noted in IGT in case of having visceral obesity and insulin resistance.

DOI: 10.1530/endoabs.32.P395

P394

Leptin and other adipocins in patients with type 2 diabetes
Andrey Verbovoy, Elena Solomonova & Anna Pashencheva
Samara State Medical University, Samara, Russia.

Aim
To evaluate leptin and other adipocins content in the blood with type 2 diabetes.

Materials and methods
Eighty six patients with type 2 diabetes were examined (59 women and 27 men) middle-aged 58.6 ± 6.4 years old. The HOMA-IR, insulin, adiponectin, resistin, leptin, and omentin levels were investigated.

Results
In patients with type 2 diabetes HOMA-IR (6.13 ± 0.81), insulin level (16.91 ± 1.86 ng/ml) is actually higher than in control group (7.78 ± 0.43 and 1.48 ± 0.11 accordingly, $P < 0.001$).

Adiponectin level in men with type 2 diabetes was evidently lower (7.5 ± 0.4 ng/ml) than in control group (10.6 ± 3.2 ng/ml, $P < 0.05$). Resistin level in type 2 diabetes was statistically higher (10.37 ± 0.55 ng/ml), than in control group (7.46 ± 0.51 ng/ml, $P < 0.01$). The lower omentin content in the patient’s blood with type 2 diabetes (264.23 ± 12.02 ng/ml) compared with the control group (395.6 ± 5.3 ng/ml, $P < 0.001$).

The leptin content in type 2 diabetes men positively correlates with insulin level ($r = 0.488$, $P < 0.05$) and HOMA-IR ($r = 0.476$, $P < 0.05$), but in type 2 diabetes women with IMB ($r = 0.652$, $P < 0.001$), WC ($r = 0.562$, $P < 0.001$) and insulin level ($r = 0.334$, $P < 0.05$).

Conclusion
The increase of leptin and resistin levels and reduction of adiponectin and omentin levels are noted in type 2 diabetes.

DOI: 10.1530/endoabs.32.P394

P396

Quality of care in diabetic patients
Mafalda Marcelino, Andreia Domingues, Armando Pereira, Dolores Passos, Joaquim Raimundo, João Silva, Luis Lopes, Maria Lopes, Paula Chambel, Valentin Santos & João Jcome de Castro
Armed Forces University Hospital, Lisbon, Portugal.

Introduction
Type 2 diabetes mellitus (T2DM) is a chronic disease, with prevalence increasing worldwide and its complications are major causes of early morbidity and mortality. Recent guidelines suggest the individualisation of glycaemic targets and glucose-lowering therapies. The aim of this study was to determine the quality of care provided to type 2 diabetic patients in our institution, analysing metabolic control, cardiovascular risk factors and prevalence of diabetic complications.

Methods
Transversal study with 423 type 2 diabetic patients, followed at our diabetes clinic.

Results
A total of 423 patients were included in the study, with a mean age of 67 ± 9.4 years. 61.7% were men. Approximately 90% of patients were overweight (41.9% obese). 65.3% had familiar history of T2DM. Mean duration of diabetes was 15 ± 10.5 years and HbA1c levels averaged 7.0 ± 1.2%. 60% had HbA1c ≤ 7% (40% HbA1c ≤ 6.5%). Concerning therapeutic regimens: 75% used oral hypoglycaemic agents (OAD) alone (73.4% of these were using two or more agents); 25% were treated with insulin (16% in combination with OAD). 82.3% of the patients had hypertension and 31.2% met the target blood pressure (BP) of 130/80 mmHg. 82.9% had dyslipidemia and 62.6% met the goal LDL cholesterol level < 100 mg/dl. 12% of patients met the combined ADA goal for BP, LDL, and HbA1c. 61.3% of the patients was anti-aggregated.Regarding diabetic complications: 16.7% had retinopathy, 26.4% nephropathy, 23% cardiovascular, and 8.7% cerebrovascular disease.

Conclusions
Metabolic control (HbA1c), BP, and LDL values were favourable in our patients, comparing to other studies. Although, it’s challenging to achieve all the goals proposed by international guidelines.

DOI: 10.1530/endoabs.32.P396
Lipid profile of patients newly diagnosed with type 2 diabetes in Albania

Florian Toti1, Aldi Shehu2, Kliti Hoti3, Manjola Carcani1, Adriana Lapardhaja1 & Luftime Bruka1

1Department of Endocrinology and Metabolic Diseases, University Hospital Center ‘Mother Theresa’, Tirana, Albania; 2Laboratory ‘Intermedica’, Tirana, Albania; 3Department of Nephrology and Dialysis, University Hospital Center ‘Mother Theresa’, Tirana, Albania.

Background and aims
Diabetic patients are at increased risk for macrovascular complications and lower extremity amputations. Knowing their metabolic control degree and lipid profile, through an early intervention, we can reduce their risk factors for cardiovascular disease, and diabetes complications. The aim of our study was to determine the lipid profile of patients newly diagnosed with type 2 diabetes.

Patients and methods
Hundred patients, selected at the outpatient policlinic no. 3 in Tirana, the capital of Albania. All the patients had completed anthropometric measures, HbA1c and lipid profile after a 12-h fast. All the persons younger than 30 years, diabetes diagnosed before 6 months, or uncompleted data were excluded from the study.

Results
We obtained all the data for 75 patients. Males 48 (64%), mean age 55.6 ± 9.92 years, mean BMI 28.7 ± 4.2 kg/m2, mean HbA1c 7.44 ± 2.54. 47.6% of the patients had a total cholesterol ≥ 220 mg/dl, 16% of the patients had triglycerides > 250 mg/dl, and 41% of them had TG < 150 mg/dl, and 64% had the LDL > 130 mg/dl. 83.3% of males had HDL < 45 mg/dl and 100% of women had HDL < 55 mg/dl respectively.

Conclusions
In our study the lipid profile of Albanian patients was somehow different from the common profile of patients newly diagnosed with T2 diabetes. Even in the previous studies we have found a lipid profile with high total cholesterol levels, and especially very low HDL levels, probably due to the sedentary lifestyle, which needs further evaluation, because the metabolic control of our patients was not very bad.

DOI: 10.1530/endoabs.32.P397

Glycemic and lipid profile in patients with acute pancreatitis

Andreae Maric, Masa Bel, Miljenka Igrec, Mihajlo Kovacic, Ivana Marodi, Luka Kuzat, Bozidar Potják & Marina Gradiser

County Hospital Cakovec, Cakovec, Croatia.

Introduction
Early hyperglycemia in acute pancreatitis (AP) is prognostic sign of severe attack. Elevated lipid levels are one of the major risk factors for AP. The objective of this work was to evaluate the glycemic and lipid profile in patients (pts) with acute pancreatitis, treated in our institution.

Methods
A total of sixty nine pts with AP were admitted to a Department of Internal medicine, from January to December 2012. At admission, plasma glucose concentration, total cholesterol serum level, triglyceride level, HDL cholesterol and LDL cholesterol level were measured. In patients with no previously known DM, and plasma glycemia concentration at admission ≥ 7.8 mmol/l (14 pts), the fasting plasma glycemia (FPG) and glycemia monitoring during hospitalization were performed. In pts with persistent FPG ≥ 6.1 mmol/l, the oral glycemia tolerance test was done 1–2 days before hospital discharge.

Results
Of sixty nine patients studied, 39 pts (57%) were female. Average age of pts was 59.9 ± 18.3 years (min 25 years and max 90 years). Total cholesterol serum level was 5.13 ± 3.27 mmol/l (range 2.3–20.0 mmol/l), triglyceride 3.63 ± 12.03 mmol/l (range 0.4–63.7 mmol/l), HDL cholesterol 1.25 ± 0.48 mmol/l (range 0.5–2.4 mmol/l), LDL cholesterol 2.75 ± 1.25 mmol/l (range 0.7–4.7 mmol/l), plasma glucose concentration at admission 7.74 ± 3.05 mmol/l (range 3.6–20.2 mmol/l), and FPG at discharge 5.65 ± 2.48 mmol/l (range 4.3–10.4 mmol/l). Previously known DM was recorded in 12 pts (17.4%); before admission 6 of them were treated with insulin, five with oral medication, one patient only with diet. According to blood glycemia tests, seven pts had newly diagnosed DM type 2 (two pts on diet, three pts oral agents, and two pts requiring insulin at the discharge), and six had new impaired glycemia tolerance (IGT).

Conclusion
High percentage of pts with hyperglycemia on admission and newly diagnosed glycemic abnormalities at discharge, suggest the need of early diagnosis and appropriate treatment of this conditions.

DOI: 10.1530/endoabs.32.P398
The role of a lifestyle modification in preventing type 2 diabetes mellitus and influence it on changes serum leptin levels
Elena Shishko
Medical, Minsk, Belarus.

Aim
The aim of our study is to assess the efficacy of a lifestyle modification including altered diet composition and physical activity in preventing diabetes mellitus type 2 (DM 2) in individuals with impaired glucose tolerance and impaired fasting glucose (IGT/IFG) and influence it on changes serum leptin levels.

Materials and methods
The study included 327 patients with IGT/IFG (68 males and 258 females) 25–65 years. Patients were divided into two groups matched by sex, age, weight, and BMI. Research group included 183 patients (32 males and 150 females) who received and carried out individual recommendations of a balanced diet and physical activity. Control group included 144 patients (36 males and 108 females) who did not lifestyle modification. Related to fasting leptin (FL) concentrations by sensitive ELISA.

Results
Patients of the research group demonstrated reduction of body weight (P < 0.01). They had positive dynamics of FPG and 2-h PG concentrations also (P < 0.001). Persons of the control group had significant increase in weight and BMI and FPG and 2-h PG concentrations elevated (P < 0.05). The main novel finding was that median serum leptin in research group decreased on −23.9% (P < 0.01) and increased in control group on +27.6% (P < 0.01) among subjects with IGT. Among patients of the research group was a reduction of new care DM 2 by 11.9% and an increase in the control group by 35.1%

Conclusion
Thereby, lifestyle modifications lead to reduction not only fasting plasma glucose, postprandial glucose concentrations but and fasting leptin concentrations in individuals with IGT/IFG.

DOI: 10.1530/endoabs.32.P401

Cardiovascular risk management in the patients with type 2 diabetes mellitus
Doo-Min Kim1, Sin Gon Kim2, Donghyouk Cho3, Chong Hwa Kim4, Chul-Sik Kim5, Won-Young Lee6 & Kyu Chang Won6
1Hallym University Medical Center, Seoul, Republic of Korea; 2Korea National University Hospital, Gwangju, Republic of Korea; 3Chonnam National University Hospital, Bucheon, Republic of Korea; 4Samsung Hospital, Seoul, Republic of Korea; 5Sejong General Hospital, Seoul, Republic of Korea; 6Yeungnam University Medical Center, Daegu, Republic of Korea.

Current guidelines on cardiovascular (CV) disease prevention recommended targeted management after elevated CV risk found by many of available method even if the patient is asymptomatic. This study was performed to explore how CV high-risk is differently detected between two distinct methods: non-invasive test (NIT) and risk calculation and how the awareness of CV high-risk impacts physician and patient behavior for risk management in diabetes patient. A prospective, observational study was carried out in 22 hospitals in Korea. 622 type 2 diabetes patients aged ≥40 years were assessed by carotid ultrasound (CUS) and United Kingdom Prospective Diabetes Study (UKPDS) risk engine. CV high-risk from CUS was defined as carotid intima-media thickness ≥1 mm or plaque presence. Before and 6 months after the test, patients completed a questionnaire on health-related behaviors and physicians collected data on treatment patterns via chart review.

Among 622 (mean age, 60.02±9.50 years), 271 (43.5%) and 66 (10.6%) patients were stratified as CV high-risk from CUS and UKPDS respectively. Approximately 40% of patients at moderate and low risk from UKPDS were determined as high-risk from CUS. The awareness of high-risk from CUS altered physician’s treatment pattern (P=0.02) for managing major CV risk factors: blood pressure (BP) and lipid. Along with CUS, risk levels by UKPDS also impacted physician’s behavior: more changes of treatment pattern in high than in low risk level for BP (12.0 vs 15.6%) and lipid (13.8 vs 21.6%). Patients noted increased health-related behaviors: smoking cessation and dietary changes (P<0.005 respectively) in 6-month follow-up than before CUS and bigger in high-risk.

This study identified NIT could detect more CV high-risk patients than risk calculation. However, awareness of CV high-risk itself has a positive impact on physician and patient behavior, regardless of assessment methods. Therefore, assessing CV risks using varied methods with the patient could be better for risk management in diabetes mellitus.

DOI: 10.1530/endoabs.32.P403

Circulating endothelial progenitor cells as a predictor of clinical outcomes in diabetic patients with symptomatic chronic heart failure
Alexander Berezin & Alexander Kremzer
State Medical University, Zaporozhye, Ukraine.

Background
Recent evidence has defined that circulating endothelial progenitor cells (EPCs) might have a pivotal role in the presence of atherosclerosis, chronically diseased vessels or following acute vascular injury. We hypothesized that diabetes mellitus (DM) may be related to worsening of ischemic chronic heart failure thereby suppression of mobilization of bone marrow-derived EPCs.

The aim of this study was to evaluate predict value of circulating EPCs in ischemic chronic heart failure patients with 2 type DM in long-term follow-up. Methods sixty eight moderate-to-severe ischemic chronic heart failure (CHF) subjects (36 with 2 type DM, left ventricular ejection fraction = 42.68% (95% CI 36–51%) aged 46–62 years were enrolled to the study. Vessel-wall and plaque geometrical and compositional parameters were measured on contrast-enhanced CT angiography. Immunostaining and flow cytometric technique (FCT) were used for predictable distinguish cells subsets depended on expression of CD14, CD34, Tie-2, CD36, and VEGFR2. Circulating EPCs are defined accordingly ISHAGE criteria as CD34+/VEGFR2 positive cells in absent CD45 expression. 100 000 events were analyzed from each tube at baseline of the study. Mononuclear cells remaining after correction of classical cardiovascular risk factors, suggesting a legacy effect. DOI: 10.1530/endoabs.32.P404
were cultured for functional analysis (CFUs) after FCT. Standardized cell counts were presented as a percentage of total leukocytes, which were identified as the total number of all CD45+ cells. Observation period for the patients was 6 months.

Results
Analysis of obtained outcomes have been shown a significantly decreasing of the total CFU count and also circulating CD34+ subsets level: CD34+ < CD45 — VEGFR2 +, and CD34+ < CD45 — Tei-2 + VEGFR2 + cells in CHF patients with 2 type DM when compared with subjects without one (P<0.001).

Second type DM (HR = 6.20, 95% CI 3.11–14.10, P = 0.009), and lower CD34+ < CD45 — VEGFR2 + (HR = 4.64, 95% CI 1.99–7.36, P = 0.004) and lower CD34+ < CD45 — Tei-2 + VEGFR2 + (HR = 0.58, 95% CI 3.15–12.10, P = 0.007) were independent prognostic variables for cardiovascular outcomes (composite point included hospitalization rate, mortality rate, all cardiovascular events, worsening of CHF) within 6 months. Results did not change after adjustment for age, sex, BMI, smoke, hypercholesterolemia, arterial hypertension, NYHA functional class of CHF and previous myocardial infarction.

Conclusions
A lower of circulating EPCs defined as CD34+ < CD45 — VEGFR2 +, and CD34+ < CD45 — Tei-2 + VEGFR2 + subsets cells in ischemic CHF patients with 2 type DM might have a high predict value for further cardiovascular outcomes. These findings can be taken into consideration as supporting of hypothesis about that such cellular biomarkers can reflect potential vascular repair insufficiency in diabetic patients with CHF.

DOI: 10.1530/endoabs.32.P404

P406
The relationship between glycemic control and BNP levels in diabetic patients
Kursad Dal1, Naim Ata2, Bunyamin Yavuz1, Omer Sen1, Guler Kizilcica1, Zekeriya Aksoy1, Aslıhan Mete Yildirim1, Bulent Uygun1, Kadri Okhan Akin3, Esin Beyan1 & Deniz Taner Ertugul4
1Teaching and Research Hospital, Ankara, Turkey; 2Andirin State Hospital, Kahramanmaras, Turkey.

Background
Glycemic control affects cardiovascular risk factors positively. The purpose of this study was to assess BNP levels in patients with poor control diabetes before specific treatment for hyperthyroidism and after glycemic regulation was achieved. The study was performed in a prospective design.

Methods
The study population consisted of 79 consecutive diabetic patients with poor glycemic control. All subjects underwent transthoracic echocardiography. Levels of fasting plasma glucose, HbA1c, lipid parameters, BNP were measured before the onset of the treatment and after glycemic regulation was achieved.

Results
A significant decrease in BNP (95.0 (4.0–1807) ng/ml vs 52.0 (2.1–987.0) ng/ml, P < 0.001) levels were observed, after improving glycemic control. The decrease in BNP levels was positively correlated with the decrease in HbA1c (r = 0.345; P = 0.003) and fasting plasma glucose (r = 0.366; P = 0.002). There was no correlation between the decrease in BNP levels and the lipid parameters (P = NS).

Conclusion
We conclude that poor glycemic control may cause high BNP measurements which can lead to misdiagnosis of congestive heart failure. We suggest that glycosylated hemoglobin and fasting plasma glucose should be checked in patients with high levels of BNP in diabetes.

DOI: 10.1530/endoabs.32.P406

Introduction
Adiponectin (AdipoQ) is a known insulin sensitizing adipokine which is also present in fetal circulation. It has been postulated to play a role in the regulation of fetal growth and development together with other adipokines. The aim of the study was to determine fetal adiponectin and find its correlations with the neonatal birthweight and maternal AdipoQ.

Patients and methods
The study included 36 women with singleton pregnancy (20 diagnosed with GDM) and their 36 term neonates born by elective cesarean section. Women with chronic disorders were excluded from the study. Laboratory assessment included the routine tests (glucose and insulin concentration) and AdiopoQ level in the maternal blood and contributed to clinical outcomes. Evaluation of proMMP-1, TIMP-1 in liver and inflammation was confirmed by histology and ultrasound. Plasma levels of proMMP-1, TIMP-1 both in and outside the maternal group was determined by human adiponectin ELISA, high sensitivity, and BioVendor.

Results
Maternal AdipoQ was lower in the study group than in the control group, the median with interquartile range were 4.9 ng/ml (4.4–5.8), 5.9 ng/ml (5.1–8.0) and 7.0 ng/ml (6.7–8.3), respectively (P = 0.009). Non-alcoholic fatty liver disease (NAFLD) develops in 75–90% of patients with diabetes mellitus type 2 (DM2) and obesity (Ob). Collagen degradation is regulated by the activity of interstitial collagenases, especially matrix metalloproteinases type 1 (MMP-1). It is necessary to determine levels of tissue inhibitor of metalloproteinases-1 (TIMP-1), which regulates activity of MMP-1.

Optimisation of diagnosis and specification of prognosis of NAFLD in patients with DM2 by determination of distant fibrosis markers: MMP-1 and TIMP-1.

Methods
Patients were presented as a percentage of total leukocytes, which were identified as the CD45+ and CD45−CD34+ cells in CHF patients with 2 type DM when compared with subjects without one (P<0.001). Second type DM (HR = 6.20, 95% CI 3.11–14.10, P = 0.009), and lower CD34+ < CD45 — VEGFR2 + (HR = 4.64, 95% CI 1.99–7.36, P = 0.004) and lower CD34+ < CD45 — Tei-2 + VEGFR2 + (HR = 0.58, 95% CI 3.15–12.10, P = 0.007) were independent prognostic variables for cardiovascular outcomes (composite point included hospitalization rate, mortality rate, all cardiovascular events, worsening of CHF) within 6 months. Results did not change after adjustment for age, sex, BMI, smoke, hypercholesterolemia, arterial hypertension, NYHA functional class of CHF and previous myocardial infarction.

Conclusions
A lower of circulating EPCs defined as CD34+ < CD45 — VEGFR2 +, and CD34+ < CD45 — Tei-2 + VEGFR2 + subsets cells in ischemic CHF patients with 2 type DM might have a high predict value for further cardiovascular outcomes. These findings can be taken into consideration as supporting of hypothesis about that such cellular biomarkers can reflect potential vascular repair insufficiency in diabetic patients with CHF.

DOI: 10.1530/endoabs.32.P404

P407
Diagnostic and prognostic value of system matrix metalloproteinases-1 in patients with diabetes mellitus 2 type
Larya Zhuravlyova & Lavrinenko Olga
Kharkiv National Medical University, Kharkiv, Ukraine.

Non-alcoholic fatty liver disease (NAFLD) develops in 75–90% of patients with diabetes mellitus type 2 (DM2) and obesity (Ob). Collagen degradation is regulated by the activity of interstitial collagenases, especially matrix metalloproteinases type 1 (MMP-1). It is necessary to determine levels of tissue inhibitor of metalloproteinases-1 (TIMP-1), which regulates activity of MMP-1.

Optimisation of diagnosis and specification of prognosis of NAFLD in patients with DM2 by determination of distant fibrosis markers: MMP-1 and TIMP-1.

Methods
Four groups (grp) of patients (pts) were investigated: first grp included 30 DM2 pts without NAFLD, second grp had 20 NAFLD pts without DM2, third grp had 30 DM2 pts with NAFLD and Ob and also 20 healthy persons were examined. The diagnosis of NAFLD was confirmed by histology and ultrasound. Plasma levels of proMMP-1, TIMP-1 by ELISA method were studied.

Results
Progressive and significant increase in levels of proMMP-1, TIMP-1 both in comparison with control grp, and between grps, were revealed indicating increased severity of DM2 when accompanied by NAFLD and Ob.

Table 1

<table>
<thead>
<tr>
<th>Plasma levels</th>
<th>Control group (n=20)</th>
<th>Group 1 (n=30)</th>
<th>Group 2 (n=20)</th>
<th>Group 3 (n=20)</th>
<th>Group 4 (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>proMMP-1 (ng/ml)</td>
<td>1.4 ± 0.05</td>
<td>2.0 ± 0.096*</td>
<td>2.3 ± 0.1</td>
<td>3.1 ± 0.12±1.6*</td>
<td>3.6 ± 0.12±5*</td>
</tr>
<tr>
<td>TIMP-1 (ng/ml)</td>
<td>373 ± 1.6</td>
<td>396.0 ± 2.8*</td>
<td>407.0 ± 1.7*</td>
<td>420.0 ± 2.5±1.1*</td>
<td>442.0 ± 2.4±5*</td>
</tr>
</tbody>
</table>

*p<0.05 vs control grp, †P<0.05 vs 1grp, ‡P<0.05 vs 2 grp, §P<0.05 vs 3 grp.

Conclusions
Increase of levels of proMMP-1, TIMP-1 in DM2 pts were caused by damage of liver and contributed to clinical outcomes. Evaluation of proMMP-1, TIMP-1 in
Fibroblast growth factor 21: a new predictor of cardiovascular events in type 2 diabetes
Monika Lenart-Lipinska, Beata Matyjaszek-Matuszek, Wojciech Gernand, Janusz Solski & Andrzej Nowakowski
Department of Laboratory Diagnostics, Medical University, Lublin, Poland; Department of Endocrinology, Medical University, Lublin, Poland; Medical Laboratory LOMA, Opole, Poland.

Introduction
The course of type 2 diabetes (DM2) is linked with increased fibroblast growth factor 21 (FGF21) concentrations, however little information is available on the prognostic significance of FGF21 in DM2. The aim of the study was to assess whether FGF21 may be a predictor of cardiovascular (CV) events in patients with DM2.

Patients and methods
The study comprised 87 patients with DM2, aged 57–66 years, with the median duration of diabetes of 10 years, who were referred to the Department of Endocrinology for routine annual metabolic assessment. All the patients underwent clinical and laboratory assessment at the time of enrolment; next, the study group was observed prospectively during the period of 24 months. Serum FGF21 levels were assessed with Human FGF21 ELISA BioVendor. During a follow-up, overall mortality, CV mortality, and CV nonfatal events were registered. Cox proportional hazards regression assessed adjusted differences in CV morbidity and mortality risk.

Results
Patients were stratified according to serum FGF21 levels less than or equal to and greater than the median of 240.7 pg/ml. The groups showed no significant differences at baseline in gender distribution, diabetes duration, insulin therapy, BMI, biochemical profiles and previous CV events. At 24-month follow-up, 21 (24.1%) patients experienced a nonfatal CV event. A significantly (P=0.0013) higher incidence of the combined end point of CV morbidity and mortality was observed in the FGF21 > 240.7 pg/ml group. In the multivariate Cox proportional hazards regression model, the presence of FGF21 greater than the median value was associated with a significant increase in the risk of the combined end point of CV morbidity and mortality (HR: 4.7, 95% CI 1.67–13.24).

Conclusion
The increased FGF21 concentrations may serve as a predictor of CV events and provide a useful tool for stratification of prognosis in DM2 patients.

DOI: 10.1530/endoabs.32.P409

Diabetes and hyperglycaemia: relation with clinical outcome in the community acquired pneumonia
Vera Fernandes, Julieta Ramalho, Maria Joana Santos, Narciso Oliveira & Maria Pereira
Department of Endocrinology, Hospital of Braga, Braga, Portugal; Department of Internal Medicine, Hospital of Braga, Braga, Portugal.

Background
Community acquired pneumonia (CAP) is a common condition and a major cause of morbidity. Diabetes mellitus (DM) increases the risk and complications of infectious diseases. However, it is necessary to clarify if DM and glycemia at the time of presentation are prognostic factors in patients with CAP.

Objectives
To evaluate the relationship between DM/glycemia at the time of presentation and complications, length of stay and mortality in patients with CAP, and the relationship between glycemic control and complications in diabetics.

Methods
Observational, analytical, and retrospective study of adults admitted to our Hospital between October/2011 and March/2012, with CAP. Electronic clinical data were analyzed and telephone calls were done to assess mortality at 30 and 90 days. The χ2, Mann–Whitney, Kruskal–Wallis tests and logistic regression were used.

Results
Of the 440 included patients, 51.1% were women, 83.1% elderly and 29.3% had a prior diagnosis of DM. Of these, 48.8% had HbA1c measured (median 6.8%, 25th percentile: 6.3%, and 75th percentile: 7.8%). The median glucose was 134 mg/dl (P25: 111 mg/dl and P75: 176 mg/dl). It was shown that patients with DM were older (P=0.002), had higher severity of pneumonia, assessed by CRB-65 (P=0.025), more complications (P=0.001), and longer length of stay (P=0.001). DM proved to be a predictor of complications (P=0.008). There was no association between DM and mortality, nor between HbA1c levels and complications, length of stay and mortality. Moreover, it was verified a gradual increase of days of stay for higher glucose levels at admission (P=0.016) and a trend towards complications in patients with hyperglycemia. However, there were no statistically significant differences between glucose levels and mortality.

Conclusion
DM and hyperglycaemia on admission are associated with adverse outcome in CAP. Both are associated with prolongation of stay and DM predicts complications from CAP.

DOI: 10.1530/endoabs.32.P408

InOS, eNOS, and XOR involvement in hyperglycaemia-induced kidney injury in rats with streptozotocin diabetes mellitus
Jelizaveta Sokolovska, Sergejs Isajevs, Olga Sugoka, Larissa Baumane, Darja Isajeva, Jelena Sharipova, Ivars Kalvinš & Nikolajs Šajkste
Faculty of Medicine, University of Latvia, Riga, Latvia; Latvian Institute of Organic Synthesis, Riga, Latvia.

Introduction
Diabetic nephropathy is a major complication of diabetes mellitus. Involvement of abnormal nitric oxide (NO) production, both via nitric oxide synthase (NOS) dependent and independent pathways (for example, xantine oxoridoreductase (XOR)) has been discussed. New compounds to treat diabetic nephropathy are searched intensively, some novel dihydrotprine class drugs (DHP) have been proposed for this purpose.

Aim
To study the changes in NO concentration and expression of NOS isoforms and XOR in kidneys of diabetic rats in the early phase of diabetic nephropathy and under effect of DHP etaforon.

Methods
Diabetes mellitus in rats was induced by streptozotocin (STZ) 50 mg/kg, i. v. after a week rats were treated by etaforon 0.5 mg/kg per os for three consecutive days. Production of NO in kidneys was monitored by means of ESP spectroscopy. InOS, eNOS, and XOR mRNA and protein expression in kidneys were detected by qRT-PCR and immunohistochemistry correspondingly.

Results
Development of STZ DM was followed by a significant increase of NO production in the kidneys, which could be attenuated by etaforon (control: 2.04 ± 0.97 ng/g tissue, STZ: 15.04 ± 2.04 ng/g tissue, and STZ + etaforon: 5.52 ± 1.089 ng/g tissue). In STZ group, XOR expression was increased (STZ 27 ± 7 vs control 8 ± 2 cells/mm²; P=0.002), and normalized by etaforon (STZ + etaforon: 9.2 ± 3 cells/mm² vs STZ: 27 ± 7 cells/mm²; P=0.0006). Similar, kidney INOS protein expression increased in STZ group and was normalized by etaforon (STZ: 79 ± 15 cells/mm² vs control 11 ± 4 cells/mm²; P=0.004; STZ + etaforon 13 ± 6 cells/mm², P=0.04 vs STZ). eNOS-expression decreased in diabetic rat kidneys, etaforon attenuated the decrease.

Conclusions
Diabetic state provokes increase of NO production in rat kidneys shortly after diabetes induction and seems to be associated with hyperexpression of iNOS and XOR. These changes can be attenuated by DHP class drug etaforon.

DOI: 10.1530/endoabs.32.P410

Advanced glycation end-products inhibit insulin signaling in human granulosa cells
Christina Piperi, Efthia Papageorgiou, Eleni Kandarakis, Michael Koutsilieris & Evanthia Diamanti-Kandarakis
University of Athens Medical School, Goudi, Athens, Greece.

Introduction
AGEs have been shown to be accumulated in granulosa cell layer from human ovaries in normal and in women with polycystic ovarian syndrome (PCOS) and insulin resistance. AGEs interfere with insulin signaling pathways of several target tissues and are implicated in insulin resistance mechanisms. There is
P412 Diabetic polyneuropathy course clinical features of patients with various age of diabetes demonstration
Irina Savasteeva, Kulash Zekenova, Aleksei Malkov, Natalia Filiptsova, Anatoli Tsukanno, Margarita Jmailik & Irina Vasuhina
The Republican Research Centre for Radiation Medicine and Human Ecology, Gomel, Belarus.

Aim To single out polineuropathy development risk group. Materials and methods Four hundred and fifty patients with a more than 5 years diabetes experience were examined. For verification of a diabetic polyneuropathy the electron neuropathography was made. By a method of the immunofemertal analysis neurospecific S100 protein level was defined. Data are presented in Me (Q25; Q75) format. The importance of distinctions was estimated by Mann-Whitney’s criterion. Results At 77.3% of patients lesion n. Suralis on axonal type is confirmed. The correlation analysis revealed a direct significant correlation of level of S100 with patient’s age (r = 0.001). Moreover, S100 decreased in the membrane compartmens of KGN cells. LY294002, a specific PI3K inhibitor was applied to define PI3K-mediated phosphorylation of Akt. In addition, insulin increased glycosylated Glut-4 variants in both cytosolic and membrane compartments compared to basal levels (P < 0.001). Combined treatment of insulin and HGA increased cytosolic fraction even further and remarkably reduced Glut-4 translocation to the membrane (P < 0.001).

Conclusions AGEs presence in the ovary associated to reduced glucose uptake by granulosa cells potentially affects follicular development and contributes to the ovarian dysfunction observed in insulin-resistance states such as PCOS.

DOI: 10.1530/endobubs.32.P412

P413 Cardiovascular risk and prevalence of metabolic syndrome in LADA patients depending on thyroid autoimmunity presence
Aura Diana Reghina1,2, Madalina Constantin1, Olivia Georgescu1, Madalina Nistor3, Ramona Olaru1, Suzana Florea1 & Simona Fica1,2
1Eliaus University Hospital, Bucharest, Romania; 2University of Medicine and Pharmacy Carol Davila, Bucharest, Romania; 3NutriLife, Bucharest, Romania.

Background LADA is a form of autoimmune diabetes with a slower decline of β cell function and distinct features from type 1 and type 2 diabetes. LADA is also a very heterogenic group. Frequently LADA is associated with other autoimmune diseases especially endocrine diseases.

Aim To evaluate prevalence of thyroid autoimmunity (TA) and its impact on cardiovascular risk and metabolic syndrome in LADA patients. Materials and methods We evaluated 104 (57 females/47 males) patients with LADA (age at onset of diabetes above 30 years, presence of pancreatic antibodies, no need of insulin at least 6 months after diagnosis). Clinical and laboratory data were obtained: weight, BMI, blood pressure, waist, total cholesterol, triglycerides, HDL-cholesterol, and thyroid peroxidase antibodies (TPOAb). Presence of metabolic syndrome (MetS) was evaluated according NCEP/ATP III criteria. Patients were divided in group A with TA and group B without TA.

Results Mean age of patients was 50.5±11.41 years, mean age at onset of diabetes was 44.03±10.13 years, and mean duration of diabetes was 6.5±1.15 years. TA evaluated by TPOAb was present in 30 patients (28.8%). Triglycerides were 115.17±87.8 mg/dl in group A vs 189.7±115 mg/dl in group B (P = 0.002), HDL cholesterol was 54.4±11.9 mg/dl in group A vs 45.08±14.4 mg/dl in group B (P = 0.002), total cholesterol was 186.23±40.4 mg/dl in group A vs 210.18±59.4 mg/dl in group B (P = 0.04), systolic blood pressure was 127.5±17.9 mmHg in group A vs 136.2±26.2 mmHg in group B (P = 0.05), diastolic blood pressure was 72.5±14 mmHg in group A vs 78.3±14.1 mmHg in group B (P = 0.05), prevalence of MetS was 46.6% in group A vs 64.8% in group B (P = 0.01); no statistical difference was observed for BMI.

Conclusion TA identifies a particular phenotype with lower cardiovascular risk and prevalence of metabolic syndrome among LADA patients.

DOI: 10.1530/endobubs.32.P413

P414 Endothelial dysfunction in type 2 diabetic patients; its relation with level of albuminuria and frequency of the microvascular complications
Murat Yagmur1, Julide Yagmur2, Lezzzan Keskin1 & Ibrahim Sahin1
1Endocrinology, Inonu University, Malatya, Turkey; 2Cardiology, Inonu University, Malatya, Turkey.

Introduction Both endothelial dysfunction and albuminuria have been shown to be related to cardiovascular risk. We aimed to investigate relations between endothelial dysfunction, albuminuria and frequency of the microvascular complication in type 2 diabetic patients.

Method Forty type 2 diabetic patients (24 microalbuminuria and 16 macroalbuminuria) with a mean age of 57.2±10.8 years and 25 healthy control subjects with a mean age of 54.1±9.6 years were included in the study. Endothelial function was assessed by brachial artery flow-mediated dilatation (FMD) in all subjects using high-resolution ultrasonography. The patients were evaluated in terms of microvascular complications, clinical and demographic features. Fasting plasma glucose and A1c levels were measured. Urinary albumin was assessed in 24-h urine sample.

Results The mean duration of the diabetes was 89.9±90.9 months and the mean A1c level was 10.12±1.2% in the diabetic group. All patient had either microalbuminuria (60%) or macroalbuminuria (40%). Retinopathy was observed in 27.5% and neuropathy in 57.5% of patients. Lower FMD and nitroglycerine-mediated dilatation were observed in diabetic patient compared to those of controls (14.6±2.0 vs 10.5±2.9, P < 0.0001; 15.3±5.8 vs 18.3±4.6, P = 0.016 respectively). The correlation analysis of the diabetic patients revealed that FMD was negatively correlated with the frequency of the
complications ($r = -0.33$, $P = 0.037$). Patients with macroalbuminuria had lower FMD compared to the patients with microalbuminuria ($2.9 \pm 0.7$ vs. $5.6 \pm 1.9\%$, $P < 0.0001$). Similarly, patients with retinopathy had lower FMD compared to the patients without retinopathy ($3.3 \pm 1.1$ vs. $5.0 \pm 2.0\%$, $P = 0.006$). FMD was negatively correlated with the level of albuminuria ($r = -0.43$, $P = 0.006$).

Conclusion: Endothelial dysfunction seems to be linked to the level of albuminuria, and correlated with the frequency of the complications in type 2 diabetic patients.

DOI: 10.1530/endoabs.32.P414

P415

Association between type 1 diabetes and oral health status
Anna Poplawska-Kita, Katarzyna Siewko, Piotr Szpak, Beata Król, Beata Telejko, Janusz Mysiłwiec, Wanda Stokowska, Maria Górska & Małgorzata Szelachowska
Medical University, Białystok, Poland.

Aims: We assessed periodontal status in patients with type 1 diabetes and healthy individuals in relation to their glycemic control, smoking, and inflammatory biomarkers.

Methods: Periodontal status was examined in 107 patients with type 1 diabetes and 40 controls, using oral hygiene index (OHI), community periodontal index (CPI) and teeth number. CPI values of 0–2 and 3–4 were classified as non-periododontitis and periodontitis respectively. Blood samples were analyzed for fasting glucose, HbA1c, C-reactive protein, fibrinogen, interleukin 1, and tumor necrosis factor-$\alpha$ (TNF-$\alpha$).

Results: Periodontitis was found in 15.0% of the controls and 57.9% of diabetic patients, including 40.0% of these with good metabolic control (GMC, HbA1c $\leq 6.5\%$) and 59.5% of those with poor metabolic control (PMC). Severe periodontitis was much frequent in the PMC than in the GMC group (26.0 vs 20.0%), and than in the controls (5.0%). The PMC patients had lower number of sextants with CPI 0 ($P < 0.001$) and higher number of sextants with CPI 3 ($P < 0.001$) and CPI 4 ($P < 0.01$), as well as lower teeth number ($P < 0.05$) in comparison with the controls. The patients with periodontitis had higher fibrinogen ($P < 0.01$) and TNF-$\alpha$ ($P < 0.001$) concentration, as well as higher OHI ($P < 0.001$) than had the patients without periodontitis. The number of sextants with CPI 0 correlated negatively with fibrinogen and TNF-$\alpha$ levels, whereas the number of sextants with CPI 3 correlated positively with TNF-$\alpha$ and fasting glucose level.

Conclusions: Our results suggest that poor metabolic control of diabetes together with smoking and inadequate oral hygiene increase the risk of severe periodontal destruction in patients with type 1 diabetes.

DOI: 10.1530/endoabs.32.P415

P416

Lower incidence of severe hypoglycaemia during pregnancy in a recent cohort of women with type 1 diabetes followed in a routine care setting
Lene Ringholm1,2, Ann-Lisa Secher1,4, Ulrik Pedersen-Bjergaard1, Birger Thorsteinsson1, Henrik Ulits Andersen2, Peter Damm1,7 & Elisabeth R Mathiesen1,4
1Center for Pregnant Women with Diabetes, Rigshospitalet, University Hospital of Copenhagen, Copenhagen, Denmark; 2Department of Endocrinology, Rigshospitalet, University Hospital of Copenhagen, Copenhagen, Denmark; 3Endocrinology Section, Department of Cardiology, Endocrinology and Nephrology, Hillerød Hospital, Hillerød, Denmark; 4Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark; 5Steno Diabetes Center, Gentofte, Denmark.

Introduction: To investigate whether the incidence of severe hypoglycaemia in pregnant women with type 1 diabetes can be reduced without deteriorating pregnancy outcomes in a routine care setting.

Methods/design: A new cohort (2009–2011) of 59 women receiving intensified education about the risk of severe hypoglycaemia in pregnancy was compared with an old cohort (2004–2006) of 108 women. The women entered the study at median 8 (range 5–13) weeks. Severe hypoglycaemia (requiring assistance from others) was prospectively reported in structured interviews.

Results: In the new vs old cohort HbA1c was comparable at inclusion (6.8% [5.6–10.7] vs 6.0% [4.9–10.5], $P = 0.25$). During pregnancy severe hypoglycaemia occurred in 25% ($n = 15$) vs 45% ($n = 49$), $P = 0.01$, corresponding to an incidence of 1.3 vs 2.5 events/patient-year, $P = 0.04$. Repeated severe hypoglycaemia occurred in 7% ($n = 4$) vs 31% ($n = 34$), $P = 0.003$. At inclusion a higher proportion of women in the new vs old cohort were on insulin analogues (rapid-acting 100 vs 44%, $P < 0.0001$; long-acting 53 vs 6%, $P < 0.0001$) and insulin pumps (24 vs 5%, $P = 0.0002$). Insulin dose at 8 weeks was lower in women on multiple daily injections in the new vs old cohort (0.67 IU/kg [0.3–1.4] vs 0.77 [0.4–1.7], $P = 0.02$) and similar in women on insulin pumps ([0.54 IU/kg [0.4–1.1] vs 0.59 [0.3–0.9], $P = 0.85$). Pregnancy outcomes were similar in the two cohorts. At multivariate logistic regression analysis, insulin dose at 8 weeks (OR 8.2 [95% CI: 1.6–41.9], $P = 0.01$), severe hypoglycaemia in the year preceding pregnancy (6.0 [2.6–13.7], $P < 0.0001$) and impaired hypoglycaemia awareness (4.8 [2.2–10.3], $P < 0.0001$) were associated with severe hypoglycaemia.

Conclusion: A lower incidence of severe hypoglycaemia in pregnancy without deteriorated pregnancy outcomes was observed in a routine care setting. Lower insulin dose in early pregnancy and focus on high-risk patients may contribute.

DOI: 10.1530/endoabs.32.P416

P417

Association between periodontal disease and vitamin D status in a type 1 diabetic population
Laura Ramos, Leticia Casanova, Maria Piedra, Pedro Muñoz, Maria Teresa, García-Unzueta, & Jose Antonio Amado
Hospital Marques de Valdecilla, Santander, Cantabria, Spain.

Background and aims: Periodontal disease (PD) is a chronic inflammatory condition where the key feature is the alveolar bone loss. Diabetes mellitus is a major risk factor in the occurrence of PD and vitamin D has been found to play a role in the development of diseases such as PD for its immunomodulatory and anti-inflammatory effects. The purpose of this study was to evaluate the relationship between PD and vitamin D levels in type 1 diabetic patients.

Subjects and methods: We conducted a prospective longitudinal survey since December 2010–December 2011. Type 1 diabetic patients aged between 18 and 65 years were recruited. Their periodontal status were examined, metabolic parameters were registered and 25OH(D), 1,25OH(D), and PTH were measured.

Results: A total of 59 consecutive type 1 diabetic patients were included. Periodontal examination showed: no PD in 24% of patients, gingivitis in 33%, initial PD in 25%, moderate PD in 17%, severe PD in 24% and previously treated PD in 7%. PD was significantly associated with age and systolic pressure. Serum 25(OH)D concentrations were low (<20 ng/ml) in 34.7% of patients, 2% of patients had levels below 10 ng/ml. Levels of 25(OH)D were inversely associated with PTH ($r = -0.521, P < 0.01$) and directly associated with 1,25(OH)D ($r = 0.369, P < 0.05$). In regression analysis the only variable that showed to be significantly associated with the degree of PD was 1,25(OH)D, being high levels protectors of PD (OR 0.953, 95% CI: 0.910–0.998). This means that a decrease of 10 pg/ml increases the risk of PD at 2.69 compared to individuals with 1,25(OH)D normal levels.

Conclusions: i) We found in this study high prevalence of PD in type 1 diabetic patients, only 24% of patients do not have any degree of PD.

ii) Low serum 1,25(OH)D concentrations may be associated with increased PD severity.

iii) Future studies are needed to prospectively assess the beneficial effect of vitamin D of periodontal disease.

DOI: 10.1530/endoabs.32.P417
P418
The role of cardio metabolic markers to predict carotid intima media thickness in type 2 diabetic patients
Masoume Mansouri, Kobra Omidfar, Hossein Fakhhrzadeh & Bagher Larjani
Endocrinology and Metabolism Research Institute, Tehran University of Medical Sciences, Tehran, Iran.

Introduction
The aim of this study was to investigate the cardiovascular risk factors which could predict vascular thickness in diabetic patients who did not have clinical symptom of atherosclerotic vascular disease

Method
A total of 101 type 2 diabetic patients (48 males and 53 females) with a mean age of 53.6±8.4 years were recruited in this study. CIMT were measured by B-mode ultrasonography and ankle brachial pressure index (ABI) was measured with a Doppler ultra-sound. Linear regression analysis was performed with CIMT as dependent variable and ABI and cardio metabolic risk factors as independent variables.

Result
We found that, CIMT were associated with blood pressure (β = −0.37, P = 0.01), waist circumference (β = −0.21, P = 0.03), TG (β = −0.12, P = 0.05), and ABI (β = −0.1, P = 0.07). Subsequent adjusted regression model showed, blood pressure (β = −0.37, P < 0.05), waist circumference (β = −0.21, P < 0.05), and TG (β = 0.24, P < 0.007) were identified as independent predictors of CIMT in diabetic patients and the effect of ABI didn’t exist anymore.

Conclusion
In conclusion, the present study showed that insulin resistance index and HbA1C were not potential predictors of carotid vascular thickness in type 2 diabetic patients who exposed to diabetes at least for 9 years. While waist circumference, systolic blood pressure and triglyceride were associated with CIMT in these patients.

Key Words
Carotid intima media thickness (CIMT), ankle brachial pressure index (ABI), cardio metabolic risk factors, Insulin resistance, HbA1C, type 2 diabetes.

DOI: 10.1530/endoabs.32.P418

P419
Improvement in sympathetic cardiac autonomic functions after 6 months of comprehensive yogic breathing program in patients with diabetes
V P Jyotsna, R Singla, S Ambekar, Anju Dhawan, Nandita Gupta, V Sreenivas & K K Deepak
All India Institute of Medical Sciences, New Delhi, India.

Aims and objectives
To assess the effect of Comprehensive Yogic Breathing Program on glycemic control, quality of life, and cardiac autonomic functions in diabetes.

Material and methods
This is a prospective randomized controlled intervention trial. 120 diabetes patients who were having HbA1c between 6 and 8 for atleast 6 months were selected. Oral drug dose was adjusted to keep the HbA1c between 6 and 8. Plasma fasting glucose, post prandial plasma glucose, HbA1C, quality of life, and cardiac autonomic functions were assessed in 120 diabetics. Patients were randomized into two groups, one group receiving standard therapy for diabetes (n=56) and the other group receiving standard therapy for diabetes and comprehensive yogic breathing program (n=64). Standard therapy included advice on diet, walk, and oral antidiabetic drugs. Comprehensive yogic breathing program is an interactive session in which Sudarshan kriya yoga followed by pranayam is taught by certified teacher. Change in fasting, post prandial plasma glucose, HbA1c, and quality of life were assessed. Cardiac autonomic function tests were done before and 6 months after intervention.

Results
There was a significant improvement in psychological (P=0.006) and social domains (P=0.002) and total quality of life (P=0.002) in the group practising comprehensive yogic breathing program as compared to the group following standard therapy alone. The improvement in sympathetic autonomic function was statistically significant (P=0.009) in the group following breathing program, while the change in standard group was not significant (P=0.06). The fasting plasma glucose and HbA1c comparable in both groups. The post prandial plasma glucose, decreased significantly in the group practising breathing programme.

P420
Relationship between metformin treatment and hyperlactacidemia diagnosed at the emergency room
Daniela Guelho, Isabel Paiva, Isabel Fonseca, Sofia Gouveia, Joana Saraiva, Carolina Moreno, Manuela Carvalheiro & Francisco Carrilho
Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal.

Introduction
Renal function and glucose lowering therapy, particularly metformin, influence serum lactate concentration in patients with type 2 diabetes (T2D). However, seems to be an acute precipitating event that triggers hyperlactacidemia and metabolic acidosis. This study aims to assess prevalence of hyperlactacidemia in T2D patients who presented at emergency room (ER), calculate relative risk of hyperlactacidemia in diabetics under metformin, identify predictive factors for high lactate concentration and determine influence of hyperlactacidemia in patients’ prognosis.

Methods
Prospective study of consecutive T2D patients that attended our hospital’s ER. Exclusion criteria: organ transplantation, pregnancy, metastatic malignancy, HIV, pheochromocytoma, alcoholism, convulsions, severe hypoxemia, hemodynamic instability, severe hepatic dysfunction or any known cause of metabolic acidosis. Selected as controls non-diabetic patients observed during same period. Studied variables: age, sex, cause of visit, blood pressure, arterial blood gas analyses with lactate, glucose, creatinine, ALT, AST, GGT, C-reactive protein, drugs, history of heart failure, pulmonary disease or obesity, and destination. Statistical analysis was performed using SPSS 21.0.

Results
Total of 221 patients, 83 (37.6%) non-diabetics and 138 (62.4%) diabetics, of these 65 (47.1%) treated with metformin. Mean serum lactate and prevalence of hyperlactacidemia were significantly higher in T2D patients relatively to control group (2.1 ± 0.1 vs 1.1 ± 0.1, P < 0.01 and 39.1 vs 3.6%, P < 0.01 respectively), and in T2D patients under metformin compared to diabetics without this drug (2.7 ± 0.2 vs 1.6 ± 0.1, P < 0.01 and 56.9 vs 23.3%, P < 0.01 respectively). T2D patients on metformin presented a 25-fold increased risk of hyperlactacidemia (OR = 25.10, P < 0.05). Creatinine level was the only independent predictive factor for lactate increased concentrations (β = 1.33, P < 0.05). Patients with hyperlactacidemia had 4.4 higher odds of being hospitalized or die (OR = 4.37, P < 0.05).

Conclusions
T2D patients, particularly those under metformin, presented significantly higher serum lactate and prevalence of hyperlactacidemia. Creatinine level was the only independent predictive factor for lactate increased concentrations. Hyperlactacidemia implies a worse prognosis and must be discarded in T2D patients observed in ER.

DOI: 10.1530/endoabs.32.P420

P421
Type 1 diabetes and pregnancy: importance of glycemic control in maternal and perinatal outcomes
Carolina Moreno1, Luisa Ruas2, Sandra Paiva1, Elvira Marta2, Sofia Gouveia1, Joana Saraiva1, Daniela Guelho1, Paulo Moura2, Manuela Carvalheiro1 & Francisco Carrilho1
1Department of Endocrinology, Diabetes and Metabolism. University Hospital of Coimbra, Coimbra, Portugal; 2Department of Obstetrics, University Hospital of Coimbra, Coimbra, Portugal.

Introduction
Type one diabetes is estimated to account for 1% of the pregnancies complicated by diabetes, associated with an increased risk of maternal and perinatal morbidity. The multidisciplinary follow up of the diabetic women can contribute to an improvement of the glycemic control, minimizing the obstetric and perinatal complications.

Aims
To characterize pregnant women with type one diabetes followed in our Department’s Endocrinology/Obstetrics Outpatient Clinic. To correlate their glycemnic control with maternal and perinatal complications.
Methods
Retrospective analysis of clinical, analytical and therapeutic data of 158 pregnant women with type one diabetes followed between 1995 and 2012. Assessment of maternal complications, type of delivery and perinatal morbidity according to their glycemic control, using SPSS 21.0.

Results
Sample of 158 women, mean age 28.7±5.3 years, with type one diabetes for 11.8±7.2 years, followed from 9.8±5.4 weeks gestation, mean A1c in the 1st Trimester = 7.7±1.5%, 2nd Trimester = 6.5±0.9% and 3rd Trimester = 6.6±0.9%.

Regarding the maternal outcomes: microvascular complications were worsened in 19 women (12.1%), only two episodes of diabetic ketoacidosis (1.3%). Preterm delivery in 40 women (25.3%), pregnancy induced hypertension in 17 (10.8%), pre eclampsia in 20 (12.7%).

Perinatal morbidity was significantly higher in women with A1c > 7% in the 1st Trimester (39.4% Vs 22.5%; P=0.041), 2nd Trimester (57% Vs 27.4%; P=0.007) and 3rd Trimester (51.4% Vs 29.1%; P=0.033), when compared with women with adequate glycemic control (A1c = 6.7%). Congenital malformations were significantly more prevalent in women with A1c > 7% in the 1st Trimester (9% Vs 0%; P=0.003), 2nd Trimester (17.9% Vs 1.6%; P=0.004) and in the 3rd Trimester (11.4% Vs 1.8%; P=0.048).

There were two cases of stillbirths (1.3%) correlated with A1c > 7% in the 3rd Trimester (P=0.035).

Concerning the type of delivery, the rate of cesarean section was high (63.8%) and significantly superior in the women with excessive gestational weight gain (P<0.001).

Conclusion
The prevalence of perinatal morbidity was significantly correlated with the glycemic control in all three trimesters, stressing the importance of a tight and permanent follow up of the pregnant women with type one diabetes.

DOI: 10.1530/endoabs.32.P421

P423
The peculiarities of atherosclerotic coronary arteries lesion in patients with coronary artery disease and type 2 diabetes mellitus

Larysa Zhuravlyova1, Natalia Lopina2 & Inna Demchenko2
1Kharkiv National Medical University, Kharkiv, Ukraine; 2Kharkiv Regional Hospital, Kharkiv, Ukraine.

Purpose
To assess the peculiarities of atherosclerotic coronary arteries (CA) lesion in patients with coronary artery disease (CAD) and type two diabetes mellitus (T2DM).

Materials and methods
We provide a retrospective analysis of 90 cases of patients with CAD (54 males, aged 60.5±4.7 years). Baseline characteristics of patients included history of CAD (7.2±2.3 years). All patients were divided into two groups: 1st group – patients with concomitant T2DM (n=30), 2nd group (n=60) – patients without concomitant T2DM. The levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL), very LDL (VLDL), triglycerides (TG), high-density lipoprotein cholesterol (HDL), fasting blood glucose and level of HbA1c were determined. The presence and extent of CA occlusion were performed using coronary angiography.

Results
Among 1st group of patients in 73% cases an atherosclerotic lesion of two and three CA has been registered, which localized in the middle and distal segments of CA, in the 2nd group in 67% cases an atherosclerotic lesion of one CA has been registered (P<0.05). The degree of occlusion of the CA was significantly higher in the 1st group in which rates of TC, LDL cholesterol, TG, HbA1c were greater. The level of HbA1c positively correlated with the degree of CA occlusion (P=0.38, P<0.05). We also evaluated positive correlation between the degree of CA occlusion and the level of LDL cholesterol (r=0.56, P<0.05), and TG levels (r=0.49, P<0.05).

Conclusions
Among patients with CAD and T2DM a diffuse and widespread coronary arteries injuries are mostly registered, as well as multivessel lesions which are mainly localized in the middle and distal segments of CA. These changes were associated with significantly higher levels of LDL cholesterol, TG and lower HDL cholesterol, and parameters of carbohydrate metabolism.

DOI: 10.1530/endoabs.32.P423

P422
Assessment of glycemic control in patients with T1DM and depression

Yana Navmenova1 & Tatiana Mokhort2
1Gomel State Medical University, Gomel, Belarus; 2Belarusian State Medical University, Minsk, Belarus.

Aim
Is to determine the frequency of hypoglycemic states in patients with T1DM with and without depression.

Materials and Methods
patients with T1DM (57 men and 51 women) aged 41.15 years (34.65, 46.66) were examined, with the experience of diabetes about 11.32 years (2.80, 11.90). Depression was determined according to the scale HADS. Assessment of glycaemia was carried out with the help of daily monitoring system of glucose in intercellular fluid (CGMS).

Results
The patients were divided into two groups: 1st – patients with T1DM with depression (n=47), 2nd – patients with T1DM without depression (n=61). The HbA1C level in the first group was 9.75% (8.70, 10.45) vs 8.15% (7.50, 9.45) in the second group (Z=0.05).

The level of minimum glycemia in patients of the first group was 2.45 (2.20, 3.45) mmol/l vs 4.40 (3.50, 5.70) mmol/l in the comparison group (P<0.05); – the duration of hypoglycemia in the first group was 2% (0, 8) vs 0% (0, 0) in the comparison group (P<0.05); – the duration of hypoglycemia in the first group was 35% (79.54%) were recorded in the first group versus 18% (29.5%) in the second group (P<0.05); – there were 26 (59.1%) cases of latent hypoglycemia in the first group versus 11 (18%) in the second group (P<0.05).

The relationship between increased levels of NaHbA1C and depression was found (RC=1.50; P=0.002; 95% CI 1.15–1.94). A similar dependence was traced when assessing the frequency of episodes of latent hypoglycemia and depression level HADS (RC=1.12; P=0.0024; 95% CI 1.02–1.24).

Conclusion
The patients with T1DM and depression had a significantly higher level of HbA1C with a lower level of minimum glycemia and a long duration of hypoglycemia. Frequent hypoglycemic episodes, including latent hypoglycemia, may be the reason of decompensation.

DOI: 10.1530/endoabs.32.P422

P424
The influence of resistin on liver function in patients with diabetes mellitus type 2 and obesity

Larysa Zhuravlyova & Olena Ogneva
Kharkiv National Medical University, Kharkiv, Ukraine.

There is a need in study of resistin (R) role in the pathogenesis of nonalcoholic fatty liver disease (NAFLD) against the background of metabolic disorders.

Aim
To assess the relationship between R and indexes of enzyme and pigment metabolism in patients (pts) with NAFLD combined with diabetes mellitus (DM) type 2 and obesity (Ob).

Methods
Fifty pts with NAFLD in combination with subcompensated DM (HbA1c 8.3±1.7%) and Ob (BMI≥30 kg/m²) were examined. The control group included 20 healthy individuals. The R was determined by ELISA method. All patients underwent ultrasound investigation of liver and also liver biopsy.

Results
The level of R in pts was increased (10.0±0.11 ng/ml; P<0.001) in comparison with the control (4.87±0.11 ng/ml). The correlation was established between R and aspartate aminotransferase (r=0.57; P<0.05), alanine aminotransferase (r=0.49; P<0.05), total bilirubin (r=0.59; P<0.05), conjugated bilirubin (r=0.71; P<0.05), alkaline phosphatase (r=0.82; P<0.05).

Conclusion
The increase of resistin level can negatively affect the pathogenesis of NAFLD, amplifying the processes of cytolysis, cholestasis and fibrogenesis in patients with comorbid DM and Ob.

DOI: 10.1530/endoabs.32.P424
Risk factors and outcomes of peripheral artery disease in patients with diabetes mellitus
Lina Zabulienė1,2, Simona Pragyte1, Dalia Triponiene1, Vaidotas Zubulis1 & Arunas Grigaitis2
1Clinics of Rheumatology, Traumatology-Orthopedics and Reconstructive Surgery, Faculty of Medicine, Vilnius University, Vilnius, Lithuania; 2Department of Ophtalmology, Abant Izzet Baysal University School of Medicine, Bolu, Turkey.

Objective
To analyse features of peripheral artery disease (PAD) in patients with diabetes mellitus (DM), to determine the consequences of PAD and the risk factors for amputation.

Material and methods
Retrospective study of 925 diabetic patients (58% males, 95.6% with type 2 DM) with PAD treated in Vascular Surgery Centre in Vilnius City University Hospital in 1997–2011 was performed.

Results
Mean age was 67.99 ± 9.47 years; mean duration of having DM was 12.95 ± 9.91 years. 47.8% of patients had diabetic angiopathy, 34.9% – nephropathy, 14.6% – retinopathy and 33.7% – polyneuropathy. On admission to the hospital 56.5% of patients had intermittent claudication or permanent leg pain, 82.5% had foot defects, including gangrene or ulcer. 30% T1DM patients and 43.2% T2DM patients with foot defects were painless.

Three hundred and sixty nine patients underwent amputation: 53.4% fingers’ amputations, 29.3% below-knee amputations and 17.3% above-knee amputations. Bypass surgery was performed in 360 (39%) patients; revascularization angioplasty procedure (PTA) had 155 (17%) patients.

An average length of stay in hospital was 17.3 ± 10.80 days. Mean length of stay in the amputees group was 18.35 ± 10.39 days and it was by 2.35 days longer than after bypass surgery (P = 0.014).

Patients without leg’s pain were treated by 1.67 days longer than those who suffered pain (P = 0.014).

Previous amputation or bypass surgery predicted new amputation (accordingly odds ratio 3.15 and 1.87), but decreased accordingly 2.17 and 1.49 times odds for bypass surgery.

Conclusions
PAD predominated in male patients, age above 60 years, with T2DM, with duration of diabetes more than 10 years and multiple diabetes complications. 39.9% of the diabetic patients with PAD underwent amputations. Patients with amputation stayed in hospital longer than those with bypass surgery or PTA. Previous amputation and bypass surgery were independent risk factors for limb amputation in diabetes patients.

DOI: 10.1530/endoabs.32.P425

Early on evaluation of hearing function with transient evoked otoacoustic emissions (TEOAE) and distortion product otoacoustic emissions (DPOAE) in type 2 diabetic patients without hypertension
Oguz Dikbas1, Tayfun Apuhan1, Burcu Altunrende2, Mesut Erdurmus1, Mehmet Tousun3 & Serkan Öztürk3
1Department of Endocrinology and Metabolism, Abant Izzet Baysal University School of Medicine, Bolu, Turkey; 2Department of Otorhinolaryngology, Abant Izzet Baysal University School of Medicine, Bolu, Turkey; 3Department of Neurology, Istanbul Bilim University School of Medicine, Istanbul, Turkey; 4Department of Ophthalmology, Abant Izzet Baysal University School of Medicine, Bolu, Turkey; 5Department of Biochemistry, Abant Izzet Baysal University School of Medicine, Bolu, Turkey; 6Department of Cardiology, Abant Izzet Baysal University School of Medicine, Bolu, Turkey.

Objective
Altered hearing function in diabetic patients has been found in both pure tone audiometry and otoacoustic emissions (OAEs). We intended to evaluate the cochlear function with both DPOAE and TEOAE in patients with DM without polyneuropathy and hypertension.

Patients and methods
Study group consisted of type 2 diabetic patients and healthy control group consisted of healthy age and sex matched volunteers. Detailed ear examination, pure tone audiometry, TEOAE, and DPOAE were assessed in all volunteers. Electromyography for excluding polyneuropathy was done in patients with DM.

Ophthalmoscopic fundus examination was performed to all diabetic patients.

Results
There are not statistically significant difference between groups according to sex, gender and smoking habits (P > 0.05). Right ear TEOAE 20 kHz frequency SNR (P = 0.043), 40 kHz frequency SNR (P = 0.018) and left ear TEOAE 20 kHz frequency SNR (P = 0.002) were lower in patients with DM. Although, there are differences in respective kHz values between DM and healthy control according to TEOAE test report, there is not statistical significant difference between groups according to overall TEOAE frequencies (left ear (P = 0.837), right ear (P = 0.442). There is a statistically significant negative correlation between right ear TEOAE 20 kHz SNR (P = 0.044) and serum glucose level. Also there is a negative correlation but statistically non significant between right ear TEOAE 40 kHz SNR and retinopathy (P = 0.053). No correlations were found among duration of diabetes, HbA1c values, TEOAEs and DPOAEs.

Conclusion
This is the first study in electromyography test negative, nonalcoholic and normotensive type 2 DM patients for evaluating cochlear function with both TEOAE and DPOAE. Albeit TEOAE measurements at some frequencies were significantly reduced in patients with DM, considering all frequencies meaningful reduction of cochlear function was not observed. This suggests us that in patients with DM, cochlear function was not affected.

DOI: 10.1530/endoabs.32.P426

Maternal 75 g OGTT glucose levels as predictive factors for large-for-gestational age newborns in women with gestational diabetes mellitus
Branka Krstevska1, Sladajna Simonova2, Valentina Velkovska-Nakova3, Biljana Jovanoska1, Irfan Ahmeti1 & Gordana Pemovska1
1University Clinic of Endocrinology, Skopje, Macedonia; 2University Clinic of Gynecology and obstetrics, Skopje, Macedonia; 3Department of Cardiology, Clinical Center of Macedonia, Skopje, Macedonia.

Objective
Our goal was to investigate the effects of glucose levels from 75-g oral glucose tolerance test (OGTT) on large for gestational age (LGA) newborns in women with gestational diabetes mellitus (GDM).

Material and methods
A prospective study was undertaken in Outpatient Department of Clinics for Endocrinology, Diabetes and Metabolic Disorders. One hundred and eighteen pregnant women were prospectively screened for GDM between 24 and 28 weeks of pregnancy.

Results
From 118 pregnancies, 78 (66.1%) women were with GDM, and 40 (33.9%) without GDM. Twenty-one (30.4%) of the neonates in the GDM group were LGA from GDM pregnancies.

Conclusion
Fasting and 1-h plasma glucose levels from OGTT may predict LGA babies in women with gestational diabetes mellitus (GDM).

DOI: 10.1530/endoabs.32.P427
P428
The influence of erythropoietin therapy on renal function and proteinuria level in patients with early diabetic nephropathy
Ivan Pchelin & Alexander Shishkin
St Petersburg State University, St Petersburg, Russia.

Introduction
Anemia is associated with an increased risk of cardiovascular events and death in patients with diabetic nephropathy (DN). However, there are still a lot of contradictions related to the benefits and risks of anemic treatment in this group of patients due to variety of non-hematopoietic effects of erythropoietin. The aim of this study was to assess the influence of erythropoietin therapy on renal function and proteinuria in patients with early DN.

Methods
We included 36 patients with type 2 diabetes mellitus and early DN (chronic kidney disease, stages 1–3) complicated with renal anemia, not receiving hemodialysis. The main group (17 patients) received standard doses of erythropoietin-α s.c. and iron medication orally for 16 weeks. The control group (19 patients) received only oral iron medications for the same period of time. We assessed serum creatinine and urea levels, glomerular filtration rate (estimated by Cockcroft-Gault formula) and urinary protein concentrations before and after 16 weeks of treatment. The Wilcoxon non-parametric test (W) was used to compare these values in study groups.

Results
Before treatment we found the following mean values in the main and the control group, respectively (P=0.05): serum creatinine – 118.7 ± 10.1 and 115.4 ± 8.8 μmol/l, serum urea – 11.5 ± 0.9 and 10.7 ± 0.6 mmol/l, estimated glomerular filtration rate – 65.5 ± 5.2 and 63.1 ± 6.9 ml/min/1.73 m², urinary protein concentration – 0.50 ± 0.09 and 0.48 ± 0.10 g/l. After 16 weeks of treatment estimated glomerular filtration rate, creatinine and urea levels have not undergone significant changes (P>0.1). At the same time mean urinary protein concentration has significantly decreased in the main group as compared to the control group – 0.29 ± 0.05 and 0.50 ± 0.11 g/l, respectively (W=2.90; P=0.004).

Conclusion
The results suggest that comprehensive anemic therapy with erythropoietin and iron medications leads to a reduction of proteinuria level in anemic patients with early stages of DN. This beneficial effect can be taken in account when defining the indications for erythropoietin administration.

DOI: 10.1530/endoabs.32.P428

P429
The diabetic hand: a forgotten complication?
Dilek Tuzun1, Eminye Duygu Ersözlu Bozkırlı2 & Ulfet Urasvav3
1Division of Endocrinology and Metabolism, Adana Numune Training and Research Hospital, ADANA, Turkey; 2Division of Rheumatology, Adana Numune Training and Research Hospital, ADANA, Turkey; 3Department of Internal Medicine, Adana Numune Training and Research Hospital, ADANA, Turkey.

Aim
To investigate the prevalence of the most frequently occurring hand complications in 1000 type 2 diabetes mellitus patients.

Material and methods
Patients (mean age 50±9.01 years, 34 women and 24 men) who had type II DM were included as a preliminary in this study. The presence of cheiroarthropathy, Dupuytren’s contracture, tinnel sign and tendinitis was assessed. All patients were evaluated also by the Rheumatology Division. Diabetic retinopathy was assessed by direct ophthalmoscopy. Urinary albumin excretion was determined in at least two 24 h urine samples.

Results
The mean diabetic duration was 6.67±5.08 (min: 1 max: 25) years. Dupuytren’s contracture’s presence was in 5.2%, cheiroarthropathy in 15.5%, tunnel sign in 15.5% and tendinitis in 6.9%. Retinopathy was present in 10.3% nephropathy in 8.6%. Mean HbA1c was 8.54 ± 1.89. Mean fasting glucose was 178.19±66.03 mg/dl. The mean urinary albumin excretion was 40.79 ± 14.92 mg/day. Mean creatinine clearance was 104.78±33.98 ml/min. The relationship between these complications and patients’ age, sex, duration of diabetes and glycaemic control was also analysed. There was positive correlation between age and tendinitis and Dupuytren’s contracture (P=0.024, r=297 and P=0.020, r=305 respectively). There was positive correlation between diabetic duration and diabetic retinopathy (P=0.026, r=295). There was positive correlation between diabetic duration and cheiroarthropathy and tendinitis (P=0.044, r=268 and P=0.012, r=332 respectively). There was positive correlation between diabetic nephropathy and cheiroarthropathy and tunnel sign (P=0.00, r=547 and P=0.003, r=377, respectively). There was positive correlation between urinary albumin excretion and cheiroarthropathy and tunnel sign (P=0.00, r=652 and P=0.000, r=477, respectively).

Conclusions
Some musculoskeletal disorders are more prevalent in type 2 diabetes mellitus patients and this may be associated with duration of diabetes. Also, the hand abnormalities were associated with the diabetic complications. Long-term prospective randomised controlled trials on preventing musculoskeletal complications and disability in diabetics are needed.

DOI: 10.1530/endoabs.32.P429

P430
Echocardiographic parameters and blood pressure in normoalbuminuric prehypertensive diabetic patients
Yilka Themeli1,2, Valbona Bajrami1, Luftile Muka1, Myftiz Barbullushi2,3, Alma Idrizi1, Daniela Teferevic1,2,3, Mahmud Shijaku1 & Albina Daka4
1DC Ikaa-Euromedica, Tirana, Albania; 2DC Med.al, Tirana, Albania; 3UHC Mother Teresa, Tirana, Albania; 4American Hospital, Tirana, Albania.

Introduction
Elevated blood pressure levels are more frequently observed in diabetic patients, than in the general population. Ambulatory blood pressure monitoring (ABPM) is better correlated with target organ damage from hypertension (HT) than clinic blood pressure readings. The correlation between ABPM and urinary albumin excretion rate (UAE) in diabetes mellitus (DM) has been found to be stronger than the correlation between clinic blood pressure (BP) and UAE.

Aim
To investigate the relation between echocardiographic parameters and 24-h ABPM in normoalbuminuric pre-hypertensive diabetic patients, without clinical evidence of nephropathy or cardiovascular autonomic nephropathy.

Methods
In our study have been enrolled 40 adult patients, 20 of them diagnosed with type 1 DM (T1DM) and 20 others with type 2 DM (T2DM). They categorized as dippers and non-dippers on the basis of 24-h ambulatory blood pressure measurement and their echocardiographic parameters were compared. An oscillographic portable monitor took 24-h BP measurements automatically.

A comprehensive echocardiographic evaluation was performed focusing on the left ventricular (LV) dimensions, LV mass index (LVMi), relative wall thickness (RWT), left atrial (LA) dimension and LV ejection fraction.

Results
Of the 20 T1DM pre-hypertensive patients, 9 were categorized as dippers and 11 as non-dippers, while of the 20 T2DM pre-hypertensive patients, 12 were categorized as dippers and 8 as non-dippers. There were no differences between the dippers and the non-dippers T1DM pre-hypertensive patients about the age, gender, body mass index (BMI) and clinical and ABPM for average day-time systolic and diastolic blood pressure levels. According to type 2 diabetic pre-hypertensive patients, there were differences about all above parameters. LV internal diameters, LV septal and posterior wall thicknesses, LV ejection fraction (LVEF) were all similar in both groups. Left atrial diameter and LVMi were found higher in the non-dippers diabetic patients. RWT resulted higher in the non-dippers patients.

Conclusion
Among pre-hypertensive normoalbuminuric diabetic patients evaluated by ABPM, echocardiographic parameters disorders resulted more frequent in T2DM. The most important conclusion of this study was that non-dippers had higher LVMi and left atrial dimensions compared with dippers. This may be a predictor of worse long term cardiovascular outcomes in non-dippers.

DOI: 10.1530/endoabs.32.P430

P431
Relationship between endothelin-1 levels in diabetics with and without microangiopathy and control subjects
Maria Rosa Villar Vicente1, Carmen Alameda2, Antonio Becerra1, Miriam Menacho3, Gilberto Perez Lopez1, Noemi G Perez de Villar1, Azucena Rodriguez1,2, Emilia Cancer1 & Gloria Canovas1
1Hospital Universitario Fuenlabrada (MADRID), Fuenlabrada (MADRID), Spain; 2Hospital Infanta Sofia, Madrid, Spain; 3Hospital Universitario Ramón y Cajal, Madrid, Spain; 4Hospital Comarcal De Melilla, Melilla, Spain.

Introduction
Among pre-hypertensive normoalbuminuric diabetic patients evaluated by ABPM, echocardiographic parameters disorders resulted more frequent in T2DM. The most important conclusion of this study was that non-dippers had higher LVMi and left atrial dimensions compared with dippers. This may be a predictor of worse long term cardiovascular outcomes in non-dippers.
Aim
To assess ET1 levels in diabetic patients with and without microangiopathy, and compared with normal subjects, nondiabetic, without underlying vascular pathology.

Introduction
The pathophysiology of diabetic microangiopathy is complex and many important aspects of it still are not fully understood. Endothelial dysfunction is of major importance in the pathogenesis of atherosclerosis and diabetic angiopathy. ET-1 is one of the most potent vasoconstrictors described and has been suggested to be involved in the development of cardiovascular disease.

Subjects and methods
We analyzed a group of 21 diabetic patients, 8 women and 13 men, aged (X ± SD) of 81.3 ± 12.6 years (range 21–78) with an evolution of diabetes in 8.4 ± 9 years (range 1–30), 2 patients had type 1 diabetes and 19 had type 2 diabetes. The 67% was on insulin therapy and 52% had microvascular involvement. The control group were 34 persons, 21 women and 13 healthy men, aged 46 ± 21.1 years (range 26–78 years) without known pathology. Statistical analysis was carried out by SPSS. ET1 was performed by RIJA Levels.

Results
ET1 levels in diabetic patients without microvascular disease (n = 10) were 5.6 ± 3 vs 8.09 ± 2.74 pg/ml (P = 0.026) in the diabetic group affections of microangiopathy (n = 11). In the control group (n = 34) ET1 levels were 3.71 ± 1.87 pg/ml.

Conclusions
– ET1 levels in diabetic patients, predominantly type 2, with microangiopathy appear to be higher than in the group did not affect microvascular disease.
– The absence of microvascular disease raises no ET1 levels in diabetic patients compared to control subjects.
– The production and the plasma levels of ET-1 are elevated in patients with diabetes, and a positive correlation between plasma ET-1 levels and diabetic microangiopathy has been reported, suggesting a potential role of the endothelin system in the pathophysiology of vascular complications in diabetes.

References

DOI: 10.1530/endoabs.32.P431

P432
Diabetic polyneuropathy predictors
Aleksei Malkov1 & V Ponomarev2
1The Republican Research Centre for Radiation Medicine and Human Ecology, Gomel, Belarus; 2Belarusian Medical Academy of Postgraduate Education, Minsk, Belarus.

Introduction
Diabetic polyneuropathy is detected in 12.5–14.5% of patients after 5 years of falling ill.

Aim
To detect predictors of diabetic polyneuropathy development in prospective parallel open clinical research.

Methods
From 2010 to 2012, 189 patients were examined (108 men, 81 women, average age = 38 ± 7 years) with DM type 2 (82%) and type 1 (18%), without neurological complaints. We estimated the neurological state, detected vibration sensation, tactile sensitivity, pain, temperature sensitivity on legs, conducted electoneuromyography. Two subgroups were defined: i) 48 patients with sensory reply amplitude in n. suralis 10–19 mV; ii) 141 patients with sensory reply amplitude in n. suralis < 10 mV. The research was conducted twice with a year interval.

Results
In 12 months in 10 cases of the first subgroup (21%) there were complaints of numbness and pains in legs, reduction of achilles reflexes; 10 patients (21%) – reduction of vibration sensation; 1 patient (5%) – tactile sensibility reduction; 1 patient (5%) – temperature sensitivity reduction. In the second subgroup in 12 months later 58 patients (41%) complained of numbness and pains in legs, achilles reflexes reduced (P = 0.047); 58 patients (41%) had a reduction of vibration sensation (P = 0.047); 15 patients (11%) – tactile sensibility reduction (P = 0.025); 18 patients (13%) – an impaired pain sensitivity (P = 0.048).

Conclusion
Patients with DM have sensory reply amplitude < 10 mV in n. suralis when conducted electoneuromyography which is a predictor of a developing in a year distal sensory diabetic polyneuropathy.

DOI: 10.1530/endoabs.32.P432

P433
Endothelial dysfunction in diabetes mellitus
Alexander Rozhko, Elena Rodzina, Irina Savasteeva & Maria Rusalenko
Republican Research Center for Radiation Medicine, Gomel, Belarus.

Objective
To identify the frequency of occurrence of endothelial dysfunction dorsalis pedis arteries in diabetes.

Materials and methods
patients with diabetes mellitus, with no complaints of the legs were examined (aged 40.25 ± 3.12, duration of diabetes 12.50 ± 1.25). Endothelial dysfunction was studied with high-resolution ultrasound (9 MHz) and diagnosed in the absence of growth in artery diameter in response to reactive hyperemia > 10% or at the appearance of paradoxal vasoconstriction.

Results
Endothelial dysfunction was diagnosed in 39 patients (29.3%), while violation macrocirculation was confirmed in 19 patients (14.3%). Among patients with endothelial dysfunction blood flow disturbance in the arteries of the foot was diagnosed in 48.7%. The result of the discriminant analysis showed that increased levels of HbA1c > 7.5%, cholesterol > 6.5 mmol/l and triglycerides > 1.7 mmol/l increase the risk of endothelial dysfunction. The risk of endothelial dysfunction also significantly increases with disease duration > 5 years, and if there is hypertension in a case history. Total accuracy of the discriminant model was 82.5%, at P < 0.05.

Conclusion
Endothelial dysfunction is an early indicator of clinical and instrumental form of angiopathy. The presence of hypertension and the lack of compensation of carbohydrate and lipid metabolism increase the risk of endothelial dysfunction.

DOI: 10.1530/endoabs.32.P433

P434
Risk factors and diabetic foot wound classification: ten years of follow-up
Marta Nóbrega1,2, Victor Colares1,2, Roque Araú1,3, Priscilla Campelo1 & Marcos Nunes1
1Federal University of Campina Grande, Campina Grande, Paraíba, Brazil; 2College of Medical Science, Campina Grande, Paraíba, Brazil, 3Federal University of Bahia, Salvador, Bahia, Brazil.

Objective
To outline the risk factors, the epidemiological profile, and the classification of diabetes type two foot ulcer.

Methods
A prospective observational study, including all the people that sought out in a consecutive way, a tertiary diabetic foot service, from February 2002 until September 2012. At admission, the patients were examined and had their ulcers evaluated by only one observer, in accordance with the University of Texas classification.

Results
Were evaluated 973 patients. The average age was 64.6 years ± 12.6 and 52.8% of them were female. The average age of the diagnosis of diabetes was 53.9 years ± 14.2. Arterial hypertension was present in 69.4%, 38% of the patients had ischemia and 74.7% presented infection. When divided according to gender, the average age of the females was 66.4 years ± 12.4 and 62.41 years ± 12.6 (P < 0.01) for the males. The diagnostic time for the females was 11.3 years and 9.52 years for the males (P < 0.01). In the classification of the wound, the prevalence of ischemia was 38% and of infection 74.7%. Penetrating to tendon or capsule were 16.9%. Penetrating to bone or joint, were 13.8%.

Conclusions
Even though there were a higher proportion of women, the men were significantly younger and had less sickness time than the women. The prevalence of ischemia
and infection was greater than that reported in current literature (10.7 and 38%, respectively).
DOI: 10.1530/endoabs.32.P434

P435
Smoking and progression of diabetic nephropathy in type 1 diabetes mellitus
Yllka Themeli1,2, Valbona Bajrami1, Myftar Barbullushi2,3, Alma Idrizi3 & Albana Daka4
1DC Ikeda-Euromedica, Tirana, Albania; 2DC Med.al, Tirana, Albania; 3UHC Mother Teresa, Tirana, Albania; 4American Hospital, Tirana, Albania.

Aim
To investigate the association between cigarette smoking and the progression of diabetic nephropathy in type 1 diabetic patients.

Methods
A prospective, follow-up study over 1 year was conducted in a sequential sample of 30 smokers, 30 nonsmokers, and 30 ex-smokers with type 1 diabetes, hypertension, and diabetic nephropathy. Progression of renal disease was defined according to the stage of nephropathy as an increase in proteinuria or serum creatinine or a decrease in the glomerular filtration rate.

Results
Progression of nephropathy was less common in nonsmokers (10%) than in smokers (59%) and patients who had quit smoking (29%), $P>0.001$. In a stepwise logistic regression analysis, cigarette pack years, 24-h sodium excretion, and GHb were independent predictive factors for the progression of diabetic nephropathy. Because blood pressure (BP) was well controlled in these patients and most values were within a normotensive range, neither standing, sitting, nor supine BP values were associated with progression of nephropathy.

Conclusions
Cigarette smoking represents an important factor associated with progression of nephropathy in treated hypertensive type 1 diabetic patients.
DOI: 10.1530/endoabs.32.P435

P436
Association of C-reactive protein and nephropathy in type 1 diabetic patients
Volha Vasylko1 & Tatiana Mokhort2
Gomel State Medical University, Gomel, Belarus; 2Belarusian State Medical University, Minsk, Belarus.

Aim
To determine the relationship between C-reactive protein (CRP) and nephropathy in type 1 diabetic patients.

Methods
A total of 68 patients (24 women and 44 men) with type 1 diabetes aged 46.58 ± 12.23 years were studied. All subjects had BMI <35 kg/m². The levels of CRP, fasting blood glucose (FBG), triglycerides (TG), HbA1c and renal function tests were assessed. Patients were divided into 2 groups: 1) group patients with nephropathy (patients were classified as normoalbuminuric (albumin excretion rate (AER) <30 mg/24 h, n=14), microalbuminuric (AER 30–300 mg/24 h, n=38) and proteinuric (AER >300 mg/24 h, n=16) and 25 healthy subjects as a control.

Results
The duration of diabetes was 14.60 ± 7.81 years. There was significant difference between group 1 and group 2 regarding the level of CRP (4.22 ± 1.74 vs. 1.54 ± 0.31, P<0.001). We found a positive significant correlation between CRP and FBG (r=0.65, P<0.05), CRP and HbA1c (r=0.54, P<0.05) and CRP and TG (r=0.30, P<0.005) in group 1.

The multivariate linear regression analysis showed significant association CRP with AER (β=0.53, β=0.681, P=0.02).

Conclusions
The level of CRP is sensitive markers for diabetic nephropathy in type 1 diabetic patients. The further evaluation will be needed to clarify this association.
DOI: 10.1530/endoabs.32.P436

P437
Relation of high sensitive CRP and insulin resistance to retinopathy in type 2 diabetes
Shokoufeh Bonakdaran & Mohammad Ali Yaghoubi
 Mashhad University of Medical Science, Mashhad, Iran.

Background
Pathophysiology of Diabetic retinopathy is a complex process. The aim of this study was to evaluate the association between insulin resistance, high sensitive CRP level as inflammation markers and diabetic retinopathy.

Methods
In this cross-sectional, 342 patients with type 2 diabetes were selected. The following data were recorded: age, sex, duration of diabetes and type of medical treatment. HbA1c, FBG, HSCRP, lipid profiles and insulin level were measured for all patients. Ophthalmologic examination was performed for all patients by an expert ophthalmologist. Insulin resistance was calculated by HOMA-IR formula. Relation between HSCRP levels and HOMA-IR was evaluated with diabetic retinopathy.

Results
A total of 342 patients (108 male, 234 female) were enrolled. The mean age of patients was 55.05 ±9.8 years. Prevalence of diabetic retinopathy in our patients was 30.4% (21% non-proliferative retinopathy and 9.35% proliferative retinopathy). This analysis was shown that HbA1c and duration of diabetes are only independent predictive factors for diabetic retinopathy. There was a differences between the serum hsCRP levels of those with and without retinopathy, however this difference was not significant ($P=0.47$). A significant association was found between diabetic proliferative retinopathy and insulin resistance ($P<0.001$).

Conclusion
It seems, apart from known risk factors for diabetic retinopathy, insulin resistance is one of the possible factors for progression of diabetic retinopathy.

Key Words
Retinopathy, High sensitive CRP, Insulin resistance, HOMA-IR, Diabetes, Inflammation
DOI: 10.1530/endoabs.32.P437

P438
Assessment of hypoglycemia risk factors in insulin treated patients
Mouna Maiza, Emma Haouat, Zinet Turki, Hajer Kandara, Leila Ben Salem & Claude Ben Siana
National Institute of Nutrition, Tunis, Tunisia.

Achieving glycemic targets is crucial in the management of diabetes mellitus. Insulin is the most effective hypoglycemic treatment for diabetes but its use can be associated with a risk of hypoglycemia.

The aim of this study is to specify risk factors of hypoglycemia in insulin-treated patients.

Patients and methods
This transversal study included 69 patients. They were females in 49.4% of cases ($n=41$). Mean age was 52 years (14 – 77). Diabetes was a type 2 diabetes in 65.2% of cases ($n=45$), a type 1 in 24.6% ($n=17$) and a secondary diabetes in 10.1% ($n=7$). Mean duration of diabetes was 13.9 years (2–32). Mean HBA1c was 10.9% (6.7 to 17.7%). Mean insulin dose was 0.78 IU/kg per day (0.14–1.7).

All patients had a normal renal function.

Hypoglycemia occurred in 81.2% of patients. Mean frequency of moderate and severe hypoglycemia were respectively 14.8 and 3.5 per month. No correlation was found between gender and type of diabetes on one hand and the occurrence of hypoglycemia on the other hand. No difference in daily insulin doses and number of daily injections was observed between patients with and without hypoglycemia. Lipodystrophies and injections into lipodystrophies were more frequent in patients with hypoglycemia but with no significant difference ($P=0.08$). Occurrence of hypoglycemia was negatively correlated to education for the technique of insulin injection ($P=0.086$) and positively correlated to duration of diabetes ($P=0.012$) and to duration of treatment with insulin ($P<0.001$).

Conclusion
Hypoglycemia in insulin-treated patients is frequent. Long progression period of diabetes and the lack of education concerning insulin injections seem to be major risk factors of hypoglycemia.
DOI: 10.1530/endoabs.32.P438
Admissions of diabetic patients due to hypoglycemia of external cause in a central hospital from 2006 to 2012

Ricardo Fonseca & João Sequeira Duarte
Centro Hospitalar Lisboa Ocidental, Hospital Egas Moniz, Lisboa, Portugal.

Background
Hypoglycemia is a common complication of Diabetes Mellitus treatment, especially in patients receiving intensive therapy. It can cause severe clinical consequences and is an obstacle to achieve glycemic targets.

Methods
Retrospective study of severe hypoglycemia due to insulin or oral drug therapy that lead to hospitalization in a central hospital. We reviewed the medical records in the last 7 years (2006–2012) for blood glucose levels at admission and pre-hospital care. A1c, diabetes duration, current therapy and comorbidities. There were 242 inpatient hospitalizations of 228 patients. We compared the hypoglycemic rate and the most commonly prescribed class of oral agents and insulin.

Results
The mean age of our patients was 76 (53–93) years, duration of hospitalization was 11 (1–123) days and 3 died in the hospital. In those with hypoglycemia as the main diagnostic (n = 132), 5.7% had diabetes mellitus type 1 and 94.3% type 2. Of all subjects (n = 242) 34.5% used insulin and 59.5% oral drugs (78% of them were treated with a sulfonylurea), the remaining 6% were not specified therapy. The mean blood glucose level was 36 mg/dl at pre-hospital care (7–60), at hospital admission 84 mg/dl (7–211) and mean HbA1c was 6.9% (5–13%) and 49% had HbA1c below 7%. Most patients had impaired renal function (mean creatinineemia 1.6 mg/dl (0.5–6.4)) and macrovascular disease. The hospital admissions rose from 2006 to 2010, and then decreased (assuming 24 admissions in 2007: 2008 = 121%, 2009 = 175%, 2010 = 175%, 2011 = 129%, 2012 = 100%).

Discussion and conclusion
The overall admissions due to severe hypoglycemia occurred in older patients. Also frequent was renal function impairment, HbA1c <7% and treated with insulin or a sulfonylurea. In this decade, overall incidence of admissions due to hypoglycemia in diabetic patients is falling, which match with the change of prescription pattern of oral agents (less sulfonylureas prescribed and the increased use of DPP4 inhibitors).

DOI: 10.1530/endoabs.32.P439

Ambulatory blood pressure profiles in type 2 diabetic patients

E Nelaj, E Sadiku, M Gjata & M Tase
Department of Internal Medicine, University Hospital Center, Tirana, Albania.

Introduction
Arterial hypertension is a major risk factor for micro- and macrovascular complications in type 2 diabetes. Several factors are known to influence blood pressure profile in diabetic patients, such as age, sex, body weight, diabetes duration, insulin dosage, metabolic control, and microalbuminuria. Ambulatory blood pressure monitoring (ABPM) permits the observation of blood pressure throughout day and night. ABPM is better related to end organ damage and cardiovascular morbidity from hypertension than office blood pressure readings. We used our database to study risk factors for abnormal 24-h blood pressure regulation and microalbuminuria in type 2 diabetic patients.

Methods
ABPM was performed in 102 diabetics. Individual least median squares (LMS)-SDs were calculated for diurnal and nocturnal systolic (SBP), diastolic (DBP), and mean arterial (MAP) blood pressure according to normalized values. The nocturnal blood pressure reduction (dipping) was calculated for SBP as well as DBP.

Results
In diabetes, DBP in particular was significantly elevated (SBP +0.51, DBP +0.58, MAP +0.80 LMS-SD) and dipping of SBP, DBP, and MAP was significantly reduced (P <0.0001). Age, diabetes duration, sex BMI, A1C, and insulin dose were related to altered blood pressure profiles; dipping, however, was only affected by age, female sex, and A1C. The presence of microalbuminuria was associated with nocturnal DBP (P <0.0001) and diastolic dipping (P <0.01).

Conclusions
Our observations revealed a clear link between the quality of metabolic control and altered blood pressure regulation even in patients with short diabetes duration. Nocturnal blood pressure in particular seems to mainly contribute to diabetes complications such as microalbuminuria.

DOI: 10.1530/endoabs.32.P440

Studying the effect of hypertriglyceridemia and hyperglycemia on the outcome of pregnancy in diabetics and non diabetics

Ahmad Saad AL-Deen, Assmaa Ahmad, Ghada AL-Sagheer, Saad AL-Gelany & Lamia ahmad
AL Minia University Hospital, AL Minia, Egypt.

Background
Wide range of biochemical and hematological laboratory values changed during diabetic pregnancy comparable to physiological pregnancies. hyperglycemia is a risk factor for fetal macrosomia. The level of maternal triglycerides have been strongly correlated with excess fetal growth and large for gestational age.

Aim of the study
The aim of this study is to evaluate the effect of maternal hyperglycemia and triglycerides on pregnancy outcome in diabetics and non diabetics. The end points are birth weight, mode of delivery, incubator admission and fetal hyper-bilirubinemia.

Patient and methods
We studied the outcome of pregnancy in 60 pregnant women (30 diabetics and 30 non diabetics). Triglyceride above 180 mg/dl after 20 weeks of gestation is considered abnormal.

Results
Pregnant diabetics with higher TG have higher incidence of CS (15 vs 5 cases P value 0.005), more macrosomic babies (6 vs 1 case P value 0.01) and higher incubator admission (12 vs 1 P value 0.002) than nondiabetics. The combined effect of high TG and hyperglycemia significantly increases the CS, incubator admission and fetal weight in pregnant diabetic than the nondiabetic with normal TG and blood glucose with P values 0.003, 0.001 and 0.001 respectively. Macrosomic babies and CS is more in diabetic with HbA1c ≤7% than nondiabetics (P 0.001, 0.003 respectively).

Table 1

<table>
<thead>
<tr>
<th>Clinical data</th>
<th>Normal TG, no = 15</th>
<th>High TG, no = 15</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVD</td>
<td>1 (6.7%)</td>
<td>0 (0%)</td>
<td>0.1</td>
</tr>
<tr>
<td>CS</td>
<td>14 (93.3%)</td>
<td>15 (100%)</td>
<td></td>
</tr>
<tr>
<td>Incubator admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12 (80%)</td>
<td>12 (80%)</td>
<td>0.5</td>
</tr>
<tr>
<td>No</td>
<td>3 (20%)</td>
<td>3 (20%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Neonatal jaundice</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 (20%)</td>
<td>3 (20%)</td>
<td>0.5</td>
</tr>
<tr>
<td>No</td>
<td>12 (80%)</td>
<td>12 (80%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Macrosomia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4 (26.7%)</td>
<td>6 (40%)</td>
<td>0.2</td>
</tr>
<tr>
<td>No</td>
<td>11 (73.3%)</td>
<td>9 (60%)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Conclusion
DM has a great impact on pregnancy outcome whether controlled or not. TG has synergistic effect on pregnancy outcome in presence of DM but has limited effect in the absence of DM.

Key Words
DM, pregnancy outcome, hyperglycemia, hypertriglycemia.

DOI: 10.1530/endoabs.32.P441

Severe diabetic ketoacidosis in type 2 diabetes mellitus

René Rodriguez-Gutierrez1, Emmanuel I González-Moreno2, Carlos R Camara-Lemarr2, Dania L Quintanilla-Flores3, Juan M González-Chávez1, Dionicio A Galarza-Delgado1, Héctor E Tamez-Pérez1 & José G González-González1
1Department of Internal Medicine, University Hospital UANL, Monterrey, Nuevo León, Mexico; 2Research Division, Faculty of Medicine UANL, Monterrey, Nuevo León, Mexico.

Introduction
Severe diabetic ketoacidosis (S-DKA) is a life-threatening condition requiring immediate hospitalization and treatment. Although mostly associated with type one diabetic patients, it is also a common condition in type two diabetes mellitus.
Adana, Turkey. Numune Training and Research Hospital, Department of Internal Medicine, upper extremity complaints of diabetes mellitus patients. It should also be taken DASH Questionnaire is useful instrument for measuring functional disability in Conclusions found between DASH score and diabetic nephropathy and retinopathy. P correlation between DASH score and BMI and TBF and %BF (score and cheiroarthropathy, tinnel sign and tendinitis (Fifty-eight patients (mean age 50 diabetes mellitus were excluded. Objective to analyze the impact of a specialized management on cardiovascular risk at the onset of type 2 diabetes mellitus. Material and method were analyzed 171 patients who visited our diabetes day hospital (DDH) during 2010–2011, studying the following variables: sex, age, BMI, smoking habit, arterial hypertension (de novo) previously known), antihypertensive therapy, dyslipidemia (de novo) previously known), hypolipidemic therapy, antidiabetic therapy and antithrombotic therapy. Furthermore, were measured other variables at the onset and 3 months after diagnosis of type 2 diabetes mellitus, using the paired Student’s t-test (SPSSv18.0). The cardiovascular risk calculator (UKFPS RISK ENGINE) was also performed initially and after three months of monitoring. Results the sample included 121 men (70.8%) and 50 women (29.2%), with an average age of 53.6 ± 12.6 years old. They showed a BMI of 31.6 ± 6.2 kg/m². A 40.9% of them were smokers while 14.6% were previously smokers and 44.4% non-smokers. An associated arterial hypertension was present in a 61.4% of patients (32% de novo and 68% previously known) and 48% were treated with a single agent, 39% with two agents and 6.4% with three agents. Regarding to hyperlipidemia it was observed in 72.5% (72.5% de novo, 28.5% previously known). According to the antidiabetic therapy we obtained the following data: oral monotherapy (17.4%), double oral therapy (31.1%), triple oral therapy (0.6%), basal insulin (9.6%), pre-mixed insulin (11.9%) and basal-bolus (29.3%). A 66% of patients used antigliaggregation or anticoagulation (acyclopsaliclyc acid 91%, oral anticoagulation 4.4%, double antigliaggregation 4.5%).

P444 Impact of a comprehensive management of glycemic profile, arterial hypertension and dyslipidemia on the onset of type 2 diabetes mellitus Cristóbal Morales Portillo, Ignacio Fernandez Peña, Virginia Hernando Jiménez, Clara García García, José Pérez Rodríguez, Raquel Venegas Zelaya, Isabel Serrano Olmedo & Angel Sendón Perez Hospital Virgen Macarena, Seville, Spain.

Objective To analyze the impact of a comprehensive management of glycemic profile, arterial hypertension and dyslipidemia on the onset of type 2 diabetes mellitus. Material and method were analyzed 171 patients who visited our diabetes day hospital (DDH) during 2010–2011, studying the following variables: sex, age, BMI, smoking habit, arterial hypertension, dyslipidemia (de novo) previously known), antihypertensive therapy, antidiabetic therapy and antithrombotic therapy. Furthermore, were measured other variables at the onset and 3 months after diagnosis of type 2 diabetes mellitus, using the paired Student’s t-test (SPSSv18.0). The cardiovascular risk calculator (UKFPS RISK ENGINE) was also performed initially and after three months of monitoring. Results the sample included 121 men (70.8%) and 50 women (29.2%), with an average age of 53.6 ± 12.6 years old. They showed a BMI of 31.6 ± 6.2 kg/m². A 40.9% of them were smokers while 14.6% were previously smokers and 44.4% non-smokers. An associated arterial hypertension was present in a 61.4% of patients (32% de novo and 68% previously known) and 48% were treated with a single agent, 39% with two agents and 6.4% with three agents. Regarding to hyperlipidemia it was observed in 72.5% (72.5% de novo, 28.5% previously known). According to the antidiabetic therapy we obtained the following data: oral monotherapy (17.4%), double oral therapy (31.1%), triple oral therapy (0.6%), basal insulin (9.6%), pre-mixed insulin (11.9%) and basal-bolus (29.3%). A 66% of patients used antigliaggregation or anticoagulation (acyclopsaliclyc acid 91%, oral anticoagulation 4.4%, double antigliaggregation 4.5%).

Table 1

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>Weight</th>
<th>DBP</th>
<th>TAD</th>
<th>LDLc</th>
<th>TG</th>
<th>HDLc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>10.6 ± 2.4</td>
<td>88 ± 19.3</td>
<td>127 ± 19</td>
<td>78 ± 13</td>
<td>126 ± 39</td>
<td>329 ± 54</td>
</tr>
<tr>
<td>Final</td>
<td>6.4 ± 1.1</td>
<td>87.7 ± 17.9</td>
<td>133 ± 6.2</td>
<td>75 ± 11</td>
<td>110 ± 37</td>
<td>140 ± 30</td>
</tr>
<tr>
<td>P ≤ 0.05</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>P ≤ 0.05</td>
<td>P ≤ 0.05</td>
<td>P ≤ 0.05</td>
</tr>
</tbody>
</table>

Conclusions It is essential the development of functional units to perform an education for health combined with a comprehensive and an intensive management of the associated diseases and risk factors present at the onset of type 2 diabetes mellitus, regarding to the determining clinical benefit which is obtained. DOI: 10.1530/endoabs.32.P444

P445 Monoballism associated with newly onset ketotic Hyperglycemia Dilik Ersil Soysal1, Bars Gelen1, Sezin Hizar1, Mete Pekdiker1, Ebru Tekesin1, Yesim Beckmann2 & Volkan Karakus1 1Department of Internal Medicine, University of Katip Celebi, Ataturk Research and Training Hospital, Izmir, Turkey; 2Department of Neurology, University of Katip Celebi, Ataturk Research and Training Hospital, Izmir, Turkey.

Movement disorders as the initial symptoms of diabetes mellitus are rare. Here, we describe one of these rare manifestations of primary diabetes: a case of newly diagnosed diabetes mellitus in an old age female patient with transient monoballismduring an episode of ketotic hyperglycemia. Ballism can be rapidly controlled by normalization of glycemia. Our patient had monoballism confined to her upper extremity. To our knowledge, this is the first report

Table 2

<table>
<thead>
<tr>
<th>UKFPS risk engine</th>
<th>CHD</th>
<th>Fatal CHD</th>
<th>Stroke</th>
<th>Fatal stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men Initial</td>
<td>26.4</td>
<td>14.6</td>
<td>3.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Final</td>
<td>12.0</td>
<td>4.8</td>
<td>3.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Women Initial</td>
<td>17.0</td>
<td>11.1</td>
<td>4.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Final</td>
<td>7.9</td>
<td>4.1</td>
<td>3.9</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Conclusions It is essential the development of functional units to perform an education for health combined with a comprehensive and an intensive management of the associated diseases and risk factors present at the onset of type 2 diabetes mellitus, regarding to the determining clinical benefit which is obtained. DOI: 10.1530/endoabs.32.P444

P443 Disabilities of the arm, shoulder and hand (DASH) questionnaire and diabetic complications: preliminary results Dilek Tuzun1, Emine Duygu Erozulu Bozkirli2 & Ulfet Urasvaz1 1Adana Numune Training and Research Hospital, Division of Endocrinology and Metabolism, ADANA, Turkey; 2Adana Numune Training and Research Hospital, Division of Rheumatology, ADANA, Turkey; 3Adana Numune Training and Research Hospital, Department of Internal Medicine, ADANA, Turkey.

Aim 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 two diabetes mellitus (DM) patients.

Material and methods Fifty-eight patients (mean age 50 ± 9.01 years, 34 women and 24 men) who had type II DM were included as a preliminary in this study. The presence of cheiroarthropathy, Dupuytren’s contracture, tunnel sign and tendinitis was assessed. Diabetic retinopathy was assessed by direct ophthalmoscopy. Urinary albumin excretion was determined in at least 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 biopsomeparamaters we measured were body fat percentage (%BF), total body fat (TBF) (kg) and BMI.

Results The mean diabetic duration was 6.67 ± 5.08 years. Dupuytren’s contracture was present in 5.2%, cheiroarthropathy in 15.5%, tunnel sign in 15.5% and tendinitis in 6.9%. Retinopathy was present in 10.3%, nephropathy in 8.6%. DASH score was 72.18 ± 33.02. Mean BMI was 31.57 ± 6.29. Mean TBF was 29.2 ± 11.87 kg. Mean %BF was 33.73 ± 10.14. There was positive correlation between DASH score and cheiroarthropathy, tunnel sign and tendinitis (P = 0.008, r = 0.35, P = 0.002, r = 0.46, P = 0.001, r = 0.45, respectively). There was positive correlation between DASH score and BMI and TBF and %BF (P = 0.000, r = 0.462; P = 0.002, r = 0.410; P = 0.002, r = 0.407, 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.32.P443
describing monoballism in a patient with ketotic hyperglycemia. She had a rapid symptomatic remission after correction of the hyperglycemia. Hemichorea-hemiballismus (HC-HB) constitute a neurological syndrome characterized by violent proximal involuntary movements on one side of the body, involving mainly the upper extremity (1). Focal epilepsy, transient chorea or ballism provoked by an episode of nonketotic hyperglycemia (NKH) in adults with type 2 diabetes (1-8), and ketotic hyperglycemia in children with type 1 diabetes mellitus have been reported (9). Nonketotic hyperglycemia occurs more often in women (1,3,5) and usually is associated with very high blood glucose (3). In these cases, the seizures (7) as well as the choreiform movements have resolved within days to a few weeks after normalization of blood glucose and hence, reversible metabolic derangements within the basal ganglia have often been assumed (1-4,8,9). Most of the cases have MRI changes in the putamen with high signal intensity on T1-weighted images (1-3,6,8) and variable signal characteristics ranging from hyper- to iso-, to hypo-intensity on T2-weighted images (1-3,6,8). Movement disorders as the initial symptoms of diabetes mellitus are rare (5,8). Here, we describe one of these rare manifestations of primary diabetes: a case of newly diagnosed diabetes mellitus in an old age female patient with transient monoballism during an episode of ketotic hyperglycemia.

DOI: 10.1530/endoabs.32.P445

P446

Comparison of Irbesartan and combination with Nigella sativa oil in experimental diabetic nephropathy

Volha Vasilkova1 & Tatiana Mokhort2

1Trakya University, Edirne, Turkey; 2Uludag University, Bursa, Turkey.

Aim

To determine the relationship between serum lipids with albuminuria in patients with type 2 diabetes mellitus.

Methods

A total of 150 diabetic patients both sexes aged 41.58 ± 11.33 years were studied. The levels of total cholesterol (TC), triglycerides (TG), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), VLDL-cholesterol (VLDL-C), HbA1C, and renal function tests were assessed. Patients were classified as normoalbuminuric (albumin excretion rate < 30 mg/24 h, n = 38), microalbuminuric (albumin excretion rate 30-300 mg/24 h, n = 79) and proteinuric (albumin excretion rate > 300 mg/24 h, n = 33).

Results

The duration of diabetes was 15.70 ± 8.81 years. The level of TC was significantly highest in proteinuric (6.90 ± 0.36 mmol/l), followed by microalbuminuric (5.38 ± 0.29 mmol/l) and followed by normoalbuminuric (5.22 ± 0.66 mmol/l), (P = 0.002, P = 0.0006, respectively). Patients with proteinuria had significantly higher level of LDL-C compared to the patients with normoalbuminuria (4.14 ± 0.95 vs 1.71 ± 0.47 mmol/l, P = 0.001). Patients with microalbuminuria had significantly higher level of LDL-C compared to the patients with normoalbuminuria (3.48 ± 1.19 vs 1.71 ± 0.47 mmol/l, P = 0.015), as well. The level of HbA1c in normoalbuminuric patients was significantly lower than in microalbuminuric (7.83 ± 1.12 vs 10.40 ± 1.59%, P < 0.004).

There were no significant differences in levels of TG, HDL-C, VLDL-C between patients with normoalbuminuria, microalbuminuria and proteinuria.

Conclusion

We showed that higher levels of LDL-C, cholesterol and TG were associated with microalbuminuria and proteinuria in patients with type 1 diabetes. Lowering atherosclerotic lipids may retard nephropathy progression in these patients.

DOI: 10.1530/endoabs.32.P446

P447

Association lipids with albuminuria in patients with type 1 diabetes

Volkha Vasilkova1 & Tatiana Mokhort2

1Gomel State Medical University, Gomel, Belarus; 2Belarusian State Medical University, Minsk, Belarus.

Aim

To determine the relationship between serum lipids with albuminuria in patients with type one diabetes.

Methods

To analyze the demographic and clinical characteristics of the patients treated at the onset of type two diabetes mellitus in our DDH.

Material and method

During 2010–2011 were analyzed 171 patients treated in our DDH, studying the following variables: sex, age, BMI, waist circumference, family diabetes history, microvascular and macrovascular long-term complications, smoking habit, rate of associated hypertension (de novo previously known), rate of dyslipidemia (de novo previously known), systolic blood pressure (SBP), diastolic blood pressure (DBP), LDLc, triglycerides(TG), HDLc, HbA1c. According to the HbA1c level the treatment was analyzed, using the paired T-student test to compare basal HbA1c and after 3 months of monitoring (SPSS18.0).

Results

121 men (70.8%) and 50 women (29.2%), with an average age of 53.6 ± 12.6 years old were treated in our DDH. They showed a BMI of 31.6 ± 6.2 kg/m2, with a waist circumference of 107.4 ± 13.0 cm. It was described a familial history of 68.4% of DM. At disease onset were observed 22.3% of macrovascular complications and 18.3% of microvascular complications. Smoking habit was identified in 40.9% of patients while previously smokers were 14.6% and non-smokers a 44.4% of them. Associated arteriopathy hypertension was described in 61.4% of the sample (32% de novo and 68% previously known) and associated dyslipidemia in 72.5% (72.5% de novo, 28.5% previously known). Other figures included an average SBP of 136.7 ± 21 mmHg, DBP of 78.3 ± 13.8 mmHg, LC levels of 120 ± 41.8 mg/dl, HDLC levels of 41.7 ± 13.8 mmHg and TG levels of 290 ± 94.9 mmHg. Classifying the patients depending on the antidiabetic therapy initiated we obtained the following data: Oral antidiabetic monotherapy (n = 33, HbA1c 8.6%), double oral antidiabetic therapy (n = 16, HbA1c 10.7), pre-mixed insulin (n = 20, HbA1c 11.7%) and basal-bolus (n = 49, HbA1c 12.1%). Basal HbA1c level was 10.6 ± 2.4% and after 3 months of monitoring 6.4 ± 1.1%, obtaining a 4.2% difference, clinically relevant and statistically significant.

Conclusions

Patients at the onset of type 2 diabetes mellitus have a severe cardiovascular risk. It requires a comprehensive treatment and an educative effort in order to optimize the therapy and minimize the existing risk.

Endocrine Abstracts (2013) Vol 32
It is essential the development of functional units for a comprehensive and an intensive management of the different associated diseases and present risk factors. DOI: 10.1530/endoabs.32.P448

P449

Lipid profile in type 1 diabetic patients in Kragujevac
Violeta Mladenovic1, Aleksandar Djukic1 & Sandra Sipetic2
Clinical Center-Kragujevac, Kragujevac, Serbia; 2Institute for Epidemiology, Belgrade, Serbia.

Introduction
The prevalence of hyperlipidemia in type 1 diabetes is 30 to 90%. High total cholesterol, LDL and triglyceride serum level is independent risk factor for cardiovascular disease. High prevalence of malignant atherogenic profile is alarming in type 1 diabetics (high triglyceride, low HDL). It is very often that dislipidemia is associated with diabetes and obesity, as well as hypertension, that pointed to inherited disorders.

The aim of this study is to analyse lipid profile in patients with type 1 diabetes in Kragujevac depending on gender.

Methods
This study included all patients registered in Primary Care with type 1 diabetes mellitus. We determined lipid profile: total cholesterol (Chol), LDL, HDL and triglycerides (TAG). Patients were divided according to gender.

Results
We registered 206 patients with type 1 diabetes in Kragujevac (107 men and 99 women). Anamnestically, previous lipid disorder had 8.2% patients. According to National Guideline Clinical Practice criteria: 55.5% has increased Chol level, 42.1% increased LDL, 29.1% increased TAG i % 33.3 decreased HDL cholesterol level. There is statistically significance in LDL (2.55 ± 0.75 vs 3.02 ± 1.18 mM, men vs women, P = 0.09), but there is no significance in average Chol level (4.73 ± 1.07 vs 5.01 ± 1.39 mM, men vs women, P = 0.379), TAG (1.4 ± 0.98 vs 1.41 ± 0.89 mM, P = 0.94) and HDL (1.39 ± 0.39 vs 1.42 ± 0.38 mM, P = 0.808).

Conclusion
There is some patients who know about lipid disorders, but the prevalence is high. There is statistically significantly higher LDL in women. All these results showed not satisfied liporegulation in type 1 diabetic patients.

DOI: 10.1530/endoabs.32.P449

P450

Association of type II diabetes mellitus with hepatocellular carcinoma occurrence. A case control study from Western Nepal
Dipendra Pandeya
Nepalese Army Institute of Health Sciences, Kathmandu, Nepal.

Objective
To assess the association of type II DM with hepatocellular carcinoma occurrence.

Materials and methods
It was a case control study carried out using data retrieved from the register maintained in the Department of Biochemistry of Manipal College of Medical Sciences, Pokhara, Nepal between 1st January, 2012 and 31st August, 2012. The variables collected were age, gender, HbA1c. All these biochemical parameters were analyzed in the Central Laboratory of our hospital by standard and validated methods. The One way ANOVA was used to examine the statistical significant difference between groups. The One way ANOVA was used to examine the statistical significant difference between groups. Post hoc test LSD used for the comparison of means of case groups. Odds ratios (OR) were calculated using simple logistic-regression analysis.

Results
The etiological factor for 200 patients of HCC was HBV, HCV, alcohol and cryptogenic. The highest age group belongs to etiological category of HCV with mean of 71.90 ± 3.6 (CI 69.28, 74.52) years and lowest age group belongs to etiological category of HBV with mean of 61.70 ± 5.3 (CI 57.88, 65.52) years. The mean imperative basis of HCC in present study was HCV (39.5%) and second most significant cause of HCC was alcohol (26%). Glycated haemoglobin was more in males HCC (7.9%) as compared to females (7.3%). The percentage of type II diabetes mellitus was more in HCC patients when compared to controls. This difference was statistically significant with an odd ratio of 4.63 (P < 0.001).

Conclusion
Type II DM influences incidence, risk of recurrence, overall survival, and treatment-related complications in HCC patients.

DOI: 10.1530/endoabs.32.P450

P451

HbA1c levels did not correlate with SF-36 and DQOL scores in patients with poorly controlled type 2 diabetes
Soner Cander1, 2, Ozen Oz Gul2, Oguzhan Sitki Dizdar3, Aysen Akkurt4, Metin Guclu1, Ercan Tuneceli2, Erdinc Erturk5 & Canan Ersoy5
1Bursa Sevkett Yilmaz Education and Research Hospital, Endocrinology and Metabolism, Bursa, Turkey; 2Uludag University Medical School, Endocrinology and Metabolism, Bursa, Turkey; 3Uludag University Medical School, Internal Medicine, Bursa, Turkey; 4Bursa Cekirge State Hospital, Endocrinology and Metabolism, Bursa, Turkey.

Aim
To evaluate the relationship between glycemic control and quality of life parameters in patients with poorly controlled type 2 diabetes.

Methods
Fifty patients with poorly controlled (HbA1c > 8–12%) type 2 diabetes included the study and were answered DQOL and SF-36 questionnaires to an assistant in internal medicine. HbA1c levels, age, gender, duration of diabetes, height, weight and waist–hip ratio measurements recorded at the same time.

Results
Mean age of the patients was 55.5 ± 7.5 (26 erkek/24 female) and mean duration of diabetes was 7.02 ± 2.8. Body mass index (BMI) and waist–hip ratio (W/H) means were found 29.0 ± 4.4 and 0.93 ± 0.06. DQOL and SF-36 scores were found 98.5 and 89.2, mean HbA1c was 1.2 ± 0.5 in all patients. HbA1c levels did not correlate with DQOL and SF36 scores (R = 0.06 (DQOL), –0.19 (SF36)) when Pearson’s correlation analysis performed. There were not correlations between quality of life scores and height, weight, DML, waist–hip ratio values.

Conclusion
There is no significant difference between the two groups in terms of quality of life. In our study, diabetes-related complications, education and social status of patients has not been evaluated. Only the relationship between quality of life measures with glycemic control and the values of physical parameters were examined. In our conclusion, quality of life values are generally lower in patients with poorly controlled diabetes and does not correlate with levels of glycemic control.

DOI: 10.1530/endoabs.32.P451

P452

Diabetic ketoacidosis in hospitalized patients with hypertriglyceridemia induced pancreatitis. Case control study
Dania L. Quinatilla-Flores1, Erick J. Rendón-Ramírez2, Perla R. Colunga-Pedraza3, Sergio A. Corral-Benavides3, Jesús Gallardo-Escamilla3 & Dionicio A. Galaza-Delgado1
1Department of Internal Medicine, University Hospital UANL, Monterrey, Nuevo León, Mexico; 2Research Division, Faculty of Medicine UANL, Monterrey, Nuevo León, Mexico; 3Faculty of Medicine UANL, Monterrey, Nuevo León, Mexico.

Introduction
Hypertriglyceridemia induced pancreatitis (HIP) is an uncommon condition accounting for 1–4% of cases of acute pancreatitis, mostly associated with poor glycemic control in diabetic patients. Diabetic ketoacidosis (DKA) may complicate the clinical course of HIP; however, few studies have documented this association. Our objective was to identify clinical and demographic differences between HIP patients with co-existing DKA compared to those without DKA.

Methods
Seven consecutive patients with DKA and HIP were compared with 7 age and gender paired HIP controls. We analyzed risk factors for the development of DKA, compared severity of illness, hospital length of stay, diet indications, duration of insulin treatment, and biochemical markers of pancreatitis. Statistical significance was considered if P < 0.05.

Results
DKA was associated with more severe HIP compared to non-DKA patients, with duration of DKA being 2.5 ± 2.5 vs 1 ± 1 (P = 0.009) and APACHE II 9 ± 3 vs 4 ± 2 (P = 0.004). There were no differences in previous diagnosis of diabetes mellitus (85 vs 71%, P = 1.00), length of stay (8 ± 3 vs 7 ± 2 days, P = 0.24), fasting duration (4 ± 2 vs 4 ± 1 days, P = 0.47), or duration of treatment with insulin infusion (6 ± 4 vs 3 ± 1 days, P = 0.12). Serum amylase, leukocyte levels and triglycerides did not differ in both groups (P = 0.96, 0.94 and 0.80). Insulin

DOI: 10.1530/endoabs.32.P452
P452

markers. As expected, DKA is associated with higher insulin dose during insulin infusion time as well as at discharge.

P453

Deficiency of vitamin D3 in patients with diabetic retinopathy
Olена Antonenкo, Rimма Skryпник & Юлия Komissareкo
Bогomoleet National Medical University, Kiev, Ukraine.

Diabetic retinopathy (DR), is the cause of population invalidization which is diagnosed in 30–90% of patients.

Purpose - to examine vitamin D levels in patients with diabetic retinopathy.

Materials and methods
Under our supervision, there were 48 patients (93 eyes). Among examined 26 patients had nonproliferative form DR and 19 – proliferative DR.

Results
Among the patients with type 1 diabetes 23 (52%) patients had a marked deficiency of vitamin D3. And in 48% was determined by hypovitaminosis. In type 2 diabetes in 25 (59%) patients experienced a deficiency of vitamin D3, and in 41% – hypovitaminosis. In patients defined different levels of vitamin D3, depending on the severity of diabetic retinopathy. Thus the presence of proliferative diabetic retinopathy observed moderate degree of vitamin D3 deficiency (37.5 ± 6.1). For patients with nonproliferative DR are characterized by the presence of hypovitaminosis 25(OH)D (63.9 ± 6.6).

Conclusion
For patients with the DR in type 1 diabetes observed average severity of vitamin D3 deficiency, and in type 2 diabetes – severe.

P454

A poorly controlled type 2 diabetes complicated by an episode of severe hypertriglyceridemia-induced pancreatitis
Nathalie Denecker & Katelijn Decoechez
UZ Brussel, Brussels, Belgium.

Introduction
Although it is recognised that diabetic ketoacidosis may present with abdominal pain, it remains important to exclude an underlying acute pancreatitis which may be masked due to ambiguous presentation.

Case
A 23-year old woman with a history of type 2 diabetes and non-compliance for her oral antidiabetic medication presented to the emergency department with abdominal epigastric pain and nausea starting a few hours before admission. Laboratory examination revealed a mild ketosis while an abdominal CT scan performed the following day demonstrated a severe acute pancreatitis of the body and tail (Balthazar Grade E) despite normal amylase serum levels upon admission, the absence of inflammatory signs and the presence of only mild clinical symptoms. The presence of a lactescent serum was the clue to an extremely high triglyceride level (> 10 000 mg/dl) causing the pancreatitis. The hypertriglyceridemia itself was attributed mainly to the diabetic ketoacidosis. There was no family history of hypertriglyceridemia. Treatment with i.v. insulin and hydration successfully resolved the ketoacidosis and hypertriglyceridemia and reversed the episode of acute pancreatitis.

Conclusion
The triad consisting of diabetic ketoacidosis, hypertriglyceridemia and acute pancreatitis is an unusual presentation of poorly controlled diabetes which can occur in type 1 as well as type 2 diabetic adults and children. With this unusual case we emphasize the need to perform an abdominal CT scan in case of persistent abdominal pain in ketoacidosis, especially in the presence of an hyperlipidemic serum, which can cause falsely low or normal amylase and lipase levels despite an acute pancreatitis.

P455

Self care practice among diabetic patients in Kathmandu
Radha Acharya Pandey & Pratikcha Chapagain
KUSMS, Kathmandu, Nepal.

Diabetes is expected to rise from 177 million today to 370 million in 2030. Self care is a crucial to keep the disease under control. Appropriate self care practice can keep the disease under control. The aim of the study was to find out the self care practice among diabetic patients. This is a simple descriptive cross-sectional study was done in Metropolycnic Kathmandu, Nepal. A total of 50 respondents, who met eligible criteria were purposively sampled and directly interviewed. χ2 test was used to see the association. Self care practice of the respondents of this study population was examined using the SPSS version 16.0.

Self care practice among the respondents was not satisfactory. Unsatisfactory self care practice was more than half (56.75%) among adequate knowledge respondents. Among respondents having inadequate knowledge, majority (92.31%) had unsatisfactory practice. Majority (74%) had adequate knowledge and satisfactory self care practice was done by only 34%. Thus it is concluded that satisfactory self care practice was inadequate. There was significant relationship between self care practice and knowledge regarding diabetes among respondents. Thus the study also concluded that adequate knowledge on Diabetes should be provided to the patients for satisfactory self care practice.

Key Words
Self care practice, knowledge, diabetes.

P456

Newly diagnosed diabetic patient presenting with crural infection
Merve Yilmaz1, Arzu Gedik2, Hasan Havnicoglu2, 7€v€lik Demir1, Tugba G€im€is1, U€l€k Ay€ibek€ T€um1, Mehmet Calan1, Abdurrahman Çoml€ek€i1, Serkan yener1, S€ev€nc Eras€an1 & Firat Bayraktar1
1Dokuz Eylul University Medical Faculty Endocrinology Department, Izmir, Turkey; 2Dokuz Eylul University Medical Faculty Orthopedics Department, Izmir, Turkey.

Introduction
The incidence of diabetic foot in diabetics is 5-10%. We herein aimed to share a formerly undiagnosed diabetic patient presenting with crural infection.

Case
A 48-year-old male patient, without a formerly known disease, presented to a local medical center due to spontaneously progressing ulceration on left leg. The ulcers did not improve with antibiotics in seven days and afterwards he was referred to our hospital. At admission, his plasma glucose was found high and he was hospitalized in endocrinology department with a diagnosis of new onset diabetes and diabetic foot infection. On physical examination, two distinct ulcerations with purulent discharge and necrotic component were noted at left leg: one in the calf and the other superior to medial malleole, each with a diameter of 10 cm with a Wagner classification of 3. His laboratory findings at admission and on follow-up are given in Table. Intensive insulin treatment and antibiotic therapy were started. Magnetic resonance angiography revealed stenosis in the crural arteries bilaterally and antiaggregant, anticoagulant, vasodilator and statin therapy were added. His clinical signs of infection including fever persisted despite the antibiotic therapy. The ultrasonographic and MRI evaluation of the ulceration site demonstrated abscess formation beneath those ulcers. Surgical debridement and vacuum associated closure were applied respectively. Tissue grafting was applied after the local infection subsided completely. The patient was discharged after clinical stabilization was obtained.

Table 1 Admission and post treatment laboratory

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Admission</th>
<th>Posttreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/l)</td>
<td>284.8</td>
<td>15.8</td>
</tr>
<tr>
<td>Sedimentation</td>
<td>110</td>
<td>28</td>
</tr>
<tr>
<td>White bloodcell</td>
<td>15 000</td>
<td>6600</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>13 600</td>
<td>3500 (53.7%)</td>
</tr>
<tr>
<td>FPG (mg/dl)</td>
<td>415</td>
<td>142</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.86</td>
<td>0.73</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>13.1</td>
<td>5.2</td>
</tr>
</tbody>
</table>

Kathmandu, Nepal. A total of 50 respondents, who met eligible criteria were purposively sampled and directly interviewed. χ2 test was used to see the association. Self care practice of the respondents of this study population was examined using the SPSS version 16.0.

Self care practice among the respondents was not satisfactory. Unsatisfactory self care practice was more than half (56.75%) among adequate knowledge respondents. Among respondents having inadequate knowledge, majority (92.31%) had unsatisfactory practice. Majority (74%) had adequate knowledge and satisfactory self care practice was done by only 34%. Thus it is concluded that satisfactory self care practice was inadequate. There was significant relationship between self care practice and knowledge regarding diabetes among respondents. Thus the study also concluded that adequate knowledge on Diabetes should be provided to the patients for satisfactory self care practice.

Key Words
Self care practice, knowledge, diabetes.

P456

Newly diagnosed diabetic patient presenting with crural infection
Merve Yilmaz1, Arzu Gedik2, Hasan Havnicoglu2, 7€v€lik Demir1, Tugba G€im€is1, U€l€k Ay€ibek€ T€um1, Mehmet Calan1, Abdurrahman Çoml€ek€i1, Serkan yener1, S€ev€nc Eras€an1 & Firat Bayraktar1
1Dokuz Eylul University Medical Faculty Endocrinology Department, Izmir, Turkey; 2Dokuz Eylul University Medical Faculty Orthopedics Department, Izmir, Turkey.

Introduction
The incidence of diabetic foot in diabetics is 5-10%. We herein aimed to share a formerly undiagnosed diabetic patient presenting with crural infection.

Case
A 48-year-old male patient, without a formerly known disease, presented to a local medical center due to spontaneously progressing ulceration on left leg. The ulcers did not improve with antibiotics in seven days and afterwards he was referred to our hospital. At admission, his plasma glucose was found high and he was hospitalized in endocrinology department with a diagnosis of new onset diabetes and diabetic foot infection. On physical examination, two distinct ulcerations with purulent discharge and necrotic component were noted at left leg: one in the calf and the other superior to medial malleole, each with a diameter of 10 cm with a Wagner classification of 3. His laboratory findings at admission and on follow-up are given in Table. Intensive insulin treatment and antibiotic therapy were started. Magnetic resonance angiography revealed stenosis in the crural arteries bilaterally and antiaggregant, anticoagulant, vasodilator and statin therapy were added. His clinical signs of infection including fever persisted despite the antibiotic therapy. The ultrasonographic and MRI evaluation of the ulceration site demonstrated abscess formation beneath those ulcers. Surgical debridement and vacuum associated closure were applied respectively. Tissue grafting was applied after the local infection subsided completely. The patient was discharged after clinical stabilization was obtained.

Table 1 Admission and post treatment laboratory

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Admission</th>
<th>Posttreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/l)</td>
<td>284.8</td>
<td>15.8</td>
</tr>
<tr>
<td>Sedimentation</td>
<td>110</td>
<td>28</td>
</tr>
<tr>
<td>White bloodcell</td>
<td>15 000</td>
<td>6600</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>13 600</td>
<td>3500 (53.7%)</td>
</tr>
<tr>
<td>FPG (mg/dl)</td>
<td>415</td>
<td>142</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.86</td>
<td>0.73</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>13.1</td>
<td>5.2</td>
</tr>
</tbody>
</table>
Conclusion
Diabetic foot infection is probably the most preventable complication of diabetes, with considerable risks of morbidity and mortality. Early intervention for these ulcers and metabolic problems is critical for adequate treatment success. Therefore, one should keep in mind that diabetes may be the underlying cause or the aggravating factor of a non healing foot ulcer and should evaluate these patients for presence of diabetes.

DOI: 10.1530/endoabs.32.P456

P457
Relation between psychiatric symptoms and diabetic complications: preliminary results
Dilek Tuzun1, Emine Duygu Erozgu Bozkiri2 & Ulfet Urasvaz1
1Division of Endocrinology and Metabolism, Adana Numune Training and Research Hospital, ADANA, Turkey; 2Division of Rheumatology, Adana Numune Training and Research Hospital, ADANA, Turkey; 3Department of Internal Medicine, Adana Numune Training and Research Hospital, ADANA, Turkey.

Aim
In this study, we aimed to assess psychiatric symptoms in 1000 type 2 diabetes mellitus (DM) patients.

Material and methods
Fifty-eight patients (mean age 50 ± 9.01 years, 34 women and 24 men) who had type II DM were included as a preliminary in this study. The presence of cheiroarthropathy, Dypuyten’s contracture, timel sign and tendinitis was assessed. Diabetic retinopathy was assessed by direct ophthalmoscopy. Urinary albumin excretion was determined in at least two 24-u urine samples. Beck’s Depression Inventory (BDI) and Beck’s Anxiety Inventory (BAI) were administered.

Results
The mean diabetic duration was 6.67 ± 5.08 years. Dypuyten’s contracture was present in 5.2%, cheiroarthropathy in 15.5%, timel sign in 15.5% and tendinitis in 6.9%. Retinopathy was present in 10.3%, nephropathy in 8.6%. BDI score was 14.14 ± 10.79 and BAI score was 18.05 ± 16.94. There was positive correlation between BDI score and diabetic nephropathy (P = 0.001, r = 0.441). Also there was positive correlation between BDI score and cheiroarthropathy and timel sign (P = 0.039, r = 0.276; P = 0.017, r = 0.317, respectively). Positive correlation between BAI score and diabetic nephropathy was detected (P = 0.000, r = 0.476). There was positive correlation between BAI score and cheiroarthropathy and timel sign (P = 0.005, r = 0.366; P = 0.010, r = 0.343, respectively). The suggested BDI cutoff of ≥ 17 had 81% sensitivity and 79% specificity and classified as clinically depressed. In our study BAI score ≥ 17 was classified as moderate and serious anxious. In our study, BAI score ≥ 17 was 37.9%.

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.32.P458

P458
Pelvic pain in a type 2 diabetes patient
Sunil Kumar Kota1, Lalit Kumar Meher2, Sruti Jammula1 & Kirtikumar D Modi1
1Medwin Hospital, Hyderabad, Andhra Pradesh, India; 2MKCG Medical College, Berhampur, Orissa, India; 3Roland Institute Of Pharmaceutical Sciences, Berhampur, Orissa, India.

Objective
To present a patient with long standing type 2 diabetes complaining of chronic pelvic pain, due to an uncommon cause of bilateral vas calcification.

Methods
Clinical, laboratory and radiographic data are reported on a 62-year-old diabetic presenting with chronic pelvic pain

Results
A 62-year-old man with a history of 17 years of diabetes presented with chronic dull aching, non radiating pain in the pelvis and in the region of sacal sulcus below 5th lumbar vertebra. There was a history of fever with chills and sweats, dysuria, urgency, frequency of urination. Pain was not aggravated during intercourse. There was no past history of sexually transmitted disease, frequent and extramarital sexual encounters, chronic kidney disease. Complete blood picture and routine urine examination did not reveal any evidence of infection or proteinuria. Fasting and post prandial blood sugars were 104 and 136 mg/dl with HbA1C at 6.7%. Other blood parameters including lipid profile, renal and liver function tests, serum calcium, phosphorous were all within normal limits. X ray showing anteroposterior view of pelvis revealed bilateral serpentine structures with symmetric and regular vas deferens calcification involving vas calcification.

Discussion
The causes of bilateral vas calcification include degenerative changes due to ageing, diabetes mellitus, end stage renal disease with secondary hyperparathyroidism. They give rise to regular calcifications within the muscular components of the vas with preservation of luminal patency. Causes of unilateral vas calcification include inflammatory conditions like tuberculosis, gonorrhoea, syphilis, chistosomiasis, and chronic non-specific urinary tract infections. The calcifications are intraluminal and irregular leading to partial or complete occlusion of the lumen.

Vasa differentia may calcify after relatively short duration of diabetes if the disease starts after the age of 40, whereas if the disease occurs before the age of 40, it has usually been present for at least 15 years before calcification is noted. Diabetes accelerates the process of senescent calcification of the vas deferens by augmented expression of several bone-associated proteins (e.g. osteopontin, bone sialoprotein, alkaline phosphatase, type 1 collagen, osteocalcin) that facilitate or regulate the calcification process. In addition uromeric serum upregulates osteoblast transcription factor Cbfa 1 and osteopontin expression. Diabetic patients with vasal wall calcification may also develop failure of emission, where no sperm reach the posterior urethra due to aperistalsis of the vas deferens.

Conclusion
Type 2 diabetic subjects with long standing pelvic pain and without any elicitable cause should be evaluated for this uncommon etiology of vas calcification.

DOI: 10.1530/endoabs.32.P459

P459
Marking out group of the increased risk of disorder of the mineralization of the osseous tissue at patients with diabetes
Irina Savasteeva, George Romanov, Tamara Moskvicheva, Nelliie Chernova, Elena Vaschenko, Andrei Filyustin, Victor Domantsevich, Alexander Korzhich, Margarita Jmailik & Irina Vasuhina
The Republican Research Centre for Radiation Medicine and Human Ecology, Gomel, Belarus.

The aim of this research was foot mineralization level definition by means of the two-absorbing X-ray densitometer and marking out group of the greater risk of a foot mineralization disorder development at patients with diabetes.

Materials and methods
Decrease in a foot mineralization at diabetes patients conformed a mineralization of metatarsal bones below 0.50 g/cm2 level and (or) tarsal bones below 0.69 g/cm2 level.

Results
For risk assessment of development of foot mineralization disorder of patients were divided into groups, depending on age of demonstration group DM1 was made up of patients with DM demonstrations age below 20 years; the 2nd group – demonstration of 20–30 years; the 3rd group – demonstration above 40 years. At age of demonstration of DM till 20 years the smallest indicators of foot bone mineral density (BMD) in comparison with patients of 2nd and 3rd groups are revealed.

The disease experience did not differ significantly from that of 2nd and 3rd group patients. The relative risk in 1st group exceeded 1.0 but was not significant. At further risk analysis of violation of foot mineralization (in group of patients with age demonstrations for < 20 years) the significant risk among the patients who have fallen ill aged before 14 years (OP = 1.24 (1.28–9.32)) is revealed.

Output
The significant risk among the patients who have fallen ill aged before 14 years.

DOI: 10.1530/endoabs.32.P459
P460

Postprandial hypotension is attenuable by Acarbose treatment in older adults with diabetes mellitus type 2: a randomized controlled crossover cohort study

David Harris, Chris Lockhart, Graydon Meneilly & Kenneth Madden
University of British Columbia, Vancouver, BC, Canada.

Postprandial hypotension (PPH) is common for older adults and may lead to syncpe and falls. Subjects with autonomic dysfunction, commonly those with diabetes mellitus (DM), are also at risk for PPH. Reported prevalence rates are 40% for PPH in DM patients. To date there are no reliable treatments for this condition in DM patients. It was our objective to demonstrate Acarbose, an α-glucosidase inhibitor, decreases the degree of PPH in an elderly DM cohort. Fifteen adults (nine women and six men) with average age of 75.9 years (range: 67–85.2), BMI of 28.6 kg/m² (range: 20.1–35.5), and individual history of DM type 2 (duration: 9.0 years; hemoglobin A1C 6.8%) attended a treatment and placebo session (separate days at least 2 weeks apart) in random double-blinded order. Subjects were fed a standardized meal (4°C) and then continuously monitored over 90 min for blood pressure by finometry, heart rate by electrocardiogram, and middle cerebral artery blood flow velocity by transcranial Doppler ultrasound (20-min baseline recorded for all measurements). Intravenous cannula was placed for blood glucose and catecholamine measurements. Prevalence of PPH was 86.7% in DM subjects (n = 13/15). The frequency of PPH occurring per study was 1.22 (range: 1–3) for Acarbose and 1.75 (range: 1–31) for placebo, and this difference was significant (t-test, P = 0.0359). The hemodynamic response of systolic blood pressure (SBP) and mean arterial pressure (MAP) (baseline as covariant) was significantly different for subjects given Acarbose by mixed-model repeated measures two-factor (time and treatment) analysis of variance (SBP: P = 0.0248, see figure; MAP: P = 0.0499).

The reported higher prevalence of PPH in our study warrants further investigation. This is the first study to demonstrate Acarbose attenuates PPH in older adults with DM. Our results suggest that Acarbose is a potential therapy for PPH in older adults with DM type 2.

DOI: 10.1530/endoabs.32.P460

P461

Effect of bariatric surgery on serum glucagon like peptide-1 concentration and metabolic parameters among obese type 2 diabetics

Salah El Din Shelbaya, Alaa Abbas Mostafa, Salwa Seddik, Manal M. Abu Shady, Meram M. Bekhet & Nesma Ali Ibrahim
1Endocrine Department, Ain Shams University, Cairo, Egypt; 2Surgery Department, Ain Shams University, Cairo, Egypt.

Objective
Assess the effect of bariatric surgery on serum glucagon like peptide-1 (GLP-1) concentration and metabolic and biochemical parameters pre and postoperatively.

Methods
This prospective study comprised 50 subjects divided into 3 groups. Group 1: 20 obese subjects with T2DM (BMI > 35) that underwent Roux-en-y gastric bypass surgery; Group 2: 20 lean subjects with T2DM and Group 3: 10 lean subjects as healthy controls.

Body weight, BMI and waist/hip ratio were analyzed. Fasting and 2hPP plasma glucose, HbA1c, lipid profile, fasting serum insulin and glucagon like peptide-1 (GLP-1) were tested.

For Group 1, tests were done twice, preoperative and 3 months after surgery. Insulin resistance was quantified using HOMA-IR.

Discussion

Results
Fasting GLP-1 levels were lower in group 1 subjects compared to the other 2 groups (4.33 ± 1.10 vs 5.21 ± 0.89, 6.14 ± 0.42 ng/ml, P < 0.001). 2hPP GLP-1 levels were lower in Group 1 compared to the other 2 groups respectively (4.94 ± 1.17 vs 6.04 ± 0.99, and 9.32 ± 0.97 ng/ml, P < 0.001); also the difference between groups 2 and 3 was statistically significant. Fasting and 2hPP GLP-1 levels showed significant negative correlation with all metabolic parameters except HbA1c, which showed highly significant positive correlation. In Group 1, mean preoperative BMI was 47.3 ± 4.2 vs 42.10 ± 3.05, 3 months postoperatively, FBS was 145.9 ± 19.2 vs 98.25 ± 16.03 mg/dl, 2hPP was 208.9 ± 33.2 vs 137.85 ± 14.90 mg/dl, HbA1c was 9.6 ± 7.1% and fasting insulin was 20.9 ± 7.25 µU/ml. There were increase in the 2 hPP GLP-1 levels (4.9 ± 1.2 vs 8.71 ± 9.1 ng/ml) and HbA1c (5.1 ± 0.9 vs 3.41 ± 0.95 mg/ml). The level of significance was P < 0.001 for all variables.

Conclusion
Bariatric surgery resulted in a statistically significant reduction in BMI and all metabolic parameters. 2h PP GLP-1 is low in diabetic patients. Postoperative 2hPP GLP-1 levels increased, possibly responsible for the metabolic benefits.

DOI: 10.1530/endoabs.32.P462

P462

Ileal interposition with diverted sleeve gastrectomy for treatment of type 2 diabetest

Sunil Kumar Kota, Surendra Ugalé, Neeraj Gupta & Kirtikumar D Modii
1Medwin Hospital, Hyderabad, Andhra Pradesh, India; 2Kirloskar Hospital, Hyderabad, Andhra Pradesh, India.

Objective
To prospectively evaluate the results of laparoscopic ileal interposition (II) with diverted sleeve gastrectomy (DSG) for control of type 2 diabetes mellitus (T2DM) and related metabolic abnormalities.

Methods
All patients underwent II + DSG. They had T2DM ≥ 5 years with poor glycemic control despite adequate dosage of oral hypoglycemic agents (OHAs) and/or insulin. The primary outcome was remission of diabetes (HbA1c < 6.5% without OHAs/insulin). Secondary outcomes were reduction in antidiabetic requirement and components of metabolic syndrome.

Results
We report the postoperative follow-up data of 31.1 ± 5.3 months (range: 3–26 months). There were 32 patients (male: female = 21:11) with mean age of 48.7 ± 7.8 (range, 34–66 years), duration of diabetes of 13.1 ± 5.8 years (range, 5–30 years), and preoperative body mass index of 29.1 ± 6.9 kg/m² (range: 22.4–39.5 kg/m²). They had poorly controlled diabetes with mean FBS: 236.52 ± 88.4 mg/dl, PLBS: 305.1 ± 124.3 mg/dl and HbA1c: 9.8 ± 1.8%. Sixteen patients (50%) had hypertension, while dyslipidemia and microalbuminuria was present in 12 patients (39%) each.

The mean operative time was 387 ± 94.3 minutes and the mean postoperative hospital stay was 8.8 ± 5.4 days. Intraoperative complications were noted in 4 patients (12.5%). Nausea and loss of appetite was observed in 3 patients (10%), which improved over a period of 2 weeks. At 3 months postoperative follow up, none of these patients had any complications with regards to the intraoperative and immediate postoperative events.

Twenty two patients (70.5%) had diabetes remission. Fifteen/sixteen (93%) patients had remission in hypertension. All participants had weight loss ranging between 15 and 25%. Postoperatively statistically significant decline was observed in the glycemic and lipid parameters, microalbuminuria at all intervals (P < 0.05). Patients with duration of follow up more than 6 months demonstrated to have better improvement in terms of reduction in glycemic, lipid parameters and microalbuminuria. Three patients had vitamin B12 deficiency 1 year after surgery.

Discussion
The surgery addresses the foregut and hindgut mechanisms for DM control. The DSG component restricts calorie intake and induces ghrelin (orexin) loss. It also excludes the duodenal loop, thereby negating the effect of insulin resistance promoting Rubino’s factor. II leads to earlier and rapid stimulation of interposed ileal segment by ingested food resulting in augmented GLP-1 secretion.

Conclusion
II + DSG seem to be promising procedures for control of type 2 DM and associated metabolic abnormalities.

DOI: 10.1530/endoabs.32.P462
Clinical usefulness of a bolus calculator in patients with type 1 diabetes mellitus treated with continuous subcutaneous insulin infusion (CSII)


Objective

One of the major problems related to the use of CSII, or intensive insulin regimens in general, is the calculation of accurate insulin boluses. A bolus calculator incorporated into the insulin pump, estimates the dose of insulin to be administered at the meal on the basis of the following parameters: current blood glucose, grams of carbohydrate in the meal, carbohydrate to-insulin ratio (CIR), insulin sensitivity factors (ISF), target blood glucose and quantity of insulin previously administered, hereby making calculation easier and more precise. The aim of the present study was to assess the efficacy of a bolus calculator incorporated into the insulin pump on pre and postprandial glycemic control of patients with type 1 diabetes on continuous s.c. insulin infusion, evaluating changes in insulin dose, number of boluses administered, acute complications, glycemic variability and HbA1c, and quality of life.

Material y methods

We enrolled 20 subjects (8 men/12 women) older than 18 years old (mean age: 36 ± 12 years) with type 1 diabetes patients treated for more than 12 months (time on insulin pump therapy: 50 ± 32 months) with continuous s.c. insulin infusion (Minimed 722, Medtronic). The patients received a infrared-linked glucometer (Contour Bayer) so that glycemic values were directly transmitted to the pump to be used by the bolus calculator, with possibility to download all the recorded data. We calculate basal CIR and ISF for all the patients, who received all the information for the accurate use of the bolus calculator.

The following data were evaluated baseline and after 3 months using the bolus calculator: HbA1c, daily insulin dose (Basal and bolus), number of bolus/day, acute complications. Glycemic variability was evaluated using MAGE and s.D. from SMBG information, and quality of life (DQOL). A treatment satisfaction questionnaire was also evaluated.

Results

After 3 months using the bolus calculator we observed significant changes (P< 0.05) in weight (71.8 ± 8 vs 72.9 kg),and metabolic control (HbA1C 7.7 ± 1.1 vs 7.5 ± 1%), we did not find differences in SMBG downloaded data (time in normo, hypo and hyperglycemia), s.d., MAGE, insulin daily dose, basal/bolus distribution, number of boluses/day, and DQOL. Patients were satisfied with the bolus calculator, they find this option easy to use and accurate.

Conclusions

In a group of patients treated with continuous s.c. insulin infusion the addition of the use of a bolus calculator achieved an improvement in glycemic control with decrease of HbA1c levels, without changes in other studied parameters, with a high level of satisfaction of the patients.

DOI: 10.1530/endoabs.32.P463

Effects of human insulin and insulin aspart preparations on levels of IGF1, IGFBPs and IGF1 bioactivity in patients with type 1 diabetes

Zhulin Ma1, Jens Sandahl Christiansen1, Torsten Lauritzen5, Tina Parkner2, Torben Laursen4 & Jan Frystyk1,3 Aarhus University, Aarhus, Denmark; 2Department of Clinical Biochemistry, Aarhus University Hospital, Aarhus, Denmark; 3Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark; 4Department of Pharmacology, Aarhus University, Aarhus, Denmark; 5Department of General Practice, School of Public Health, Aarhus University, Aarhus, Denmark.

Introduction

Type 1 diabetes (T1D) is characterized by primary insulin insufficiency and secondary disruption of GH–IGF–IGFBP axis. S.c. insulin therapy is necessary to normalize this axis. This study aimed to investigate whether the distinct insulin profiles obtained with insulin aspart and human insulin preparations, respectively, affect IGF1 concentration and bioactivity and IGFBP levels differently.

Methods

In a randomized, four-period crossover study, 19 patients with T1D received identical doses (0.2 U/kg s.c.) of insulin aspart, BIAsp70, or BIAsp50 immediately before a standardized meal, or human insulin 30 min before meal. Serum total IGF1, bioactive IGF1 and IGFBP1 to -3 were measured for 9 h postprandially.

Results

After equipotent doses, IGFBP-1 levels decreased significantly during the first 3 h with all insulin treatments, but the AUC of IGFBP-1 was significantly higher in the BIAsp50 group (mean [range] 351, 312–396 μg/l) as compared to insulin aspart (262, 233–294 μg/l) and human insulin (256, 228–288 μg/l, P = 0.001). Human insulin showed lower AUC of IGFBP-1 than insulin aspart preparations during 0–3, 0–6, 6–9 and 0–9 h. During the first 6 h, the four insulin preparations resulted in similar profiles and AUCs of total IGF1, bioactive IGF1, IGFBP-2 and IGFBP-3. Whereas total IGF1 remained constant, bioactive IGF1 fell at the end of the study (6–9 h), concomitant with the increase in IGFBP-1.

Conclusions

Despite distinct pharmacokinetic properties, the insulin aspart preparations had similar effects on IGF1 concentration and bioactivity, IGFBP-2 and IGFBP-3 as compared to those of human insulin, but differed in respect to IGFBP-1. Further, bioactive IGF-1 appeared to be more sensitive to insulin exposure than total IGF1.

DOI: 10.1530/endoabs.32.P464

Vitamin B12 deficiency in type 2 diabetic patients on metformin

Mitra Niafar, Behzad Jamal, Hosseyn Alikhah & Amir Bahrami Tabriz University of Medical Sciences, Tabriz, East Azerbaijan, Iran.

Introduction

Metformin is the only biguanide that is currently in use as an oral hypoglycemic agent in type 2 diabetes mellitus (DM). There are reports about the vitamin B12 deficiency in metformin users. This study aimed to evaluate the vitamin B12 deficiency in patients with type 2 DM using metformin or other hypoglycemic agents.

Methods

A descriptive-comparative study was performed on 400 patients with type 2 DM presenting to Endocrinology Clinic since Jan 2011 to Jan 2012. The enrolled patients were divided in two groups: i) those receiving metformin from 6 months ago (n = 200); and ii) those receiving hypoglycemic agents other than metformin (n = 200). Blood samples were taken from all patients after 12 h fasting and serum vitamin B12 and other variables were measured and compared between two groups.

Results

Patients receiving metformin had significantly lower Vitamin B12 levels (320.04 ± 141.34 vs 408.50 ± 175.07 pmol/l, P < 0.001) and higher prevalence of vitamin B12 deficiency (14.5 vs 2%, P < 0.001). There was negative correlation between vitamin B12 levels with weight (r = -0.18, P < 0.001) and BMI (r = -0.11, P = 0.02) and positive correlation between vitamin B12 and metformin administration (r = 0.26, P < 0.001).

Conclusion

Patients with type 2 DM under long-term metformin therapy had lower vitamin B12 levels than those under other hypoglycemic drugs. The relation between vitamin B12 deficiency and metformin therapy indicates the need for periodic measurement of serum vitamin B12 level in patients under long-term metformin therapy.

DOI: 10.1530/endoabs.32.P465

Medical staff experience and acceptance of an ICU insulin infusion protocol in a tertiary hospital in the Philippines

Queenie Ngalob, Cecilia Jimeno & Iris Thiele Inip-Tan Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, Philippine General Hospital, University of the Philippines, Manila, The Philippines.

Introduction

The recommended strategy for glycemic control among critically ill is i.v. insulin infusion protocol. Critical to its success is acceptance of the implementing staff. In our hospital, we adapted and modified the Yale insulin infusion protocol (IIP). Evaluation of medical staff experience has not yet been done.

Objectives

To evaluate medical staff experience and acceptace of the IIP through a survey and focused group discussion.

Methods

A survey followed by focused group discussions among the medical staff of the Medical and Central Intensive Care Units were done. Questionnaires were
distributed to the nurses and medical residents of ICUs. Focused group discussions were done after to clarify the information derived from the survey.

Results

One hundred nine medical staff (47 nurses and 62 medical residents) participated in the study. Majority (76.7%) of ICU nurses felt they had good knowledge of the IIP. Seventy-seven percent of nurses agree that the IIP is effective in controlling hyperglycemia and 54.7% felt that it prevented hypoglycemia. While 74.5% held that the protocol increases their workload due to frequent glucose checks and need for computations to adjust the drip, majority (64%) agree that it is easy to administer. Seventy percent of nurses are satisfied with the use of the protocol. Similarly, most (80.6%) medical residents in the ICUs believe that the IIP is effective. While most felt that the protocol is not easy to administer (68%), majority (64%) would still opt to use it for their patients. The staff believes that periodic training and provision of supplies are key factors in improving the protocol.

Conclusion

Experience and acceptance of the insulin infusion protocol is generally excellent for both nurses and physicians. Despite an increase in workload, most believe the protocol to be effective and would advocate its use for ICU patients.

DOI: 10.1530/endoabs.32.P466

P467

Efficacy and safety of 1 year treatment with Liraglutide in subjects with type 2 diabetes

Flavia Prodam1, 2, Marco Zavattaro2, Chantal Ponziani2, Lorenda Pagan2, Marina Caputo2, Gabriele Allochis, Samà Maria Teresa2, Arianna Busti2 & Gianluca Aimaretti2

1Department of Health Sciences, Novara, Italy; 2Department of Translational Medicine, Novara, Italy.

Introduction

Liraglutide, a GLP-1 analogue, is a new option for the treatment of type 2 diabetes (DM2). The purpose of this study was to evaluate the efficacy and safety of liraglutide in daily clinical practice in a heterogeneous population with DM2.

Subjects and methods

Four visits were scheduled in a 1 year study (baseline, 4, 8 and 12 months). All patients with a HbA1c not on target (>7%) during an oral hypoglycemic treatment, or patients intolerant to metformin were recruited. Exclusion criteria were: the presence of kidney diseases on dialysis, lack of compliance or refusal to treatment, or patients intolerant to metformin were recruited. Exclusion criteria were: the presence of kidney diseases on dialysis, lack of compliance or refusal to treatment, or patients intolerant to metformin were recruited. Exclusion criteria were: the presence of kidney diseases on dialysis, lack of compliance or refusal to treatment, or patients intolerant to metformin were recruited.

Results

243 subjects (110 males and 133 females) were recruited, with an age of (mean ± SD) 59.6 ± 10.4 years and a disease duration of 8.3 ± 7.0 years. Fasting blood glucose (10.3 ± 3.1 vs 8.4 ± 2.6 mmol/L, P < 0.0001) and HbA1c (8.6 ± 1.3 vs 7.4 ± 1.0%, P < 0.0001) decreased at 4 months and maintained a plateau overtime. Body weight (92.8 ± 18.9 vs 89.5 ± 18.2 kg, P < 0.0001) and BMI (33.8 ± 6.6 vs 32.3 ± 6.0 kg/m2, P < 0.0001) decreased at 4 months and then remained stable. Lipids slightly decreased over time. Total cholesterol (4.6 ± 0.9 vs 4.3 ± 0.9 mmol/L, P < 0.01), LDL-cholesterol (2.6 ± 0.8 vs 2.4 ± 0.7 mmol/L, P < 0.05) and triglycerides (1.9 ± 1.0 vs 1.7 ± 0.9 mmol/L, P < 0.03) decreased respecting to baseline, independently of glucose and HbA1c changes. Conversely, HDL cholesterol increased (1.16 ± 0.28 vs 1.17 ± 0.27 mmol/L, P < 0.01). 35 patients left the study, 3 of them because of adverse effects.

Conclusion

Liraglutide is effective in controlling DM2 in daily clinical practice. Liraglutide could have pleiotropic actions in the control of DM2.

DOI: 10.1530/endoabs.32.P467

P468

Metabolic surgery assessment score (MSAS): a tool to predict diabetes remission after modified bariatric surgery

Sunil Kumar Kota1, Lalit Kumar Meher2, Sunit Jammula3 & Kirtikumar D Modi1

1Medwin Hospital, Hyderabad, Andhra Pradesh, India; 2MKCG Medical College, Berhampur, Orissa, India; 3Roland Institute Of Pharmaceutical Sciences, Berhampur, Orissa, India.

Objective

Laparoscopic ileal interposition (II) with sleeve gastrectomy (SG)/diverted sleeve gastrectomy (DSG) are types of modified bariatric surgery for treatment of type 2 diabetes (T2DM). DSG is preferred over SG in patients with less favourable metabolic profile. Owing to variable remission response in our patients, retrospectively we devised a novel score metabolic surgery assessment score (MSAS). It helps to select the type of procedure and to predict the diabetes remission before surgery.

Methods

Forty-six patients underwent II + SG and 29 for II + DS II + DSG was performed on 29 patients. MSAS was calculated based on preoperative parameters. MSAS of the subjects with and without remission (maintaining HbA1C <6.5% without any medication) were compared.

Results

Patients subjected to II + SG had mean age of 48.3 ± 8.1 years, duration of T2DM 9.8 ± 7.6 years and body mass index (BMI) 32.1 ± 6.9 kg/m2. All patients had poorly controlled diabetes with HbA1C 9.5 ± 2.2%. Mean MSAS in patients who underwent II + SG (n = 46) was 9.2 ± 1.4. Twenty one (46%) had remission in diabetes. In the same group, patients with BMI ≥ 35 kg/m2, MSAS was 8.9 ± 1.7 and remission rate was 85%. MSAS was significantly lower in patients with remission than patients without remission (8.1 ± 0.8 vs 10.2 ± 0.9, P = 0.0001). Patients subjected to II + DSG had mean age of 48.7 ± 7.8 years, duration of T2DM 13.1 ± 5.8 years and BMI 29.1 ± 6.7 kg/m2. All patients had poorly controlled diabetes with HbA1C 9.8 ± 1.8%. Mean MSAS in patients who underwent II + DSG (n = 29) was 10.4 ± 1.3 (significantly higher than II + SG group, P = 0.0004). Twenty one (72%) had remission in diabetes. MSAS was significantly lower in patients with remission than patients without remission (9.7 ± 0.8 vs 12.0 ± 0.5, P < 0.0001).

Patients with MSAS ≥ 10 in II + SG group and MSAS ≥ 12 in II + DSG group did not get remission. MSAS was not significantly different (P = 0.1468) in patients without remission in II + SG (10.2 ± 0.9) vs patients with remission in II + DSG (9.7 ± 0.7). This indirectly suggests that DSG instead of SG would have helped them in achieving remission.

Discussion

The surgery addresses the foregut and hindgut mechanisms leading to remission in T2DM. The SG component restricts calorie intake and induces ghrelin (orexin) loss,II leads to rapid stimulation of interposed ileal segment by ingested food leads resulting in augmented GLP-1 secretion. DSG leads to better remission by exclusion of Rubino’s factor and GIP from duodenum, abolition of hedonic effect of food, earlier stimulation of ileum leading to better incretin response.

Conclusion

Preoperative MSAS can be a useful tool to select the type of surgical procedure and to predict post operative diabetes remission.

DOI: 10.1530/endoabs.32.P468

P469

No benefit for mortality but advanced risk of hypoglycemia with intensive glucose control in critical care unit brain injured patients: a meta-analysis of RCTs

Klio Chantzirara1, Christos Maniatis2, Panagiotis Kokkoris3 & Georgios Toloulonis3

1Department of Endocrinology, Diabetes and Metabolism, Evangelismos General Hospital of Athens, Athens, Greece, 2Department of Cardiology, Hellenic Red Cross Hospital of Athens, Athens, Greece, 3Department of Endocrinology, 251 Hellenic Air Force General Hospital of Athens, Athens, Greece.

Background

Acute stroke, traumatic brain injury, and subarachnoid hemorrhage are common diagnoses of patients in Critical Care Units, which often lead to increased morbidity and mortality. Patients with brain damage experience wide glucose fluctuations, with episodes of hyperglycemia. Hyperglycemia has traditionally been associated with poor clinical outcomes after brain injury.

Objectives

To evaluate the effects of intensive versus conventional glucose control in mortality as well as the incidence of glucose disturbances and the neurologic outcome in critically ill brain injured adults.

Search methods

We performed a meta-analysis after systematically searching PubMed, and Scopus databases to retrieve RCTs in English. We initially retrieved 3081 citations. After removing duplicates, animal, pediatric, and studies including non ICU patients, eleven studies remained and were analyzed with Review Manager ver 5.1. Odds ratios (OR) or Peto Odds ratios (POR) with 95% confidence intervals (CI) were calculated.

Results

In critically ill adult patients, both in-hospital mortality, OR 1.05 (M-H, Fixed, 95%, CI 0.60, 1.85) and overall mortality, OR 1.09 (M-H, Fixed,
Method
Fifty patients with a diagnosis of type 2 diabetes receiving oral antidiabetic drug therapy and glycemic control did not provide were included the study. Insulin detemir was begun 0.1–0.2 U/kg daily dose, half of the patients started with a single daily dose and the other half with same dose twice daily. At the end of the twelfth week, the groups were crossing. Insulin doses were titrated every 2 weeks for 24 weeks according to capillary blood glucose including in the morning and in the evening levels.

Results
Fifty patients completed the study, mean age was 55.5 years (M/F: 26/24), mean duration of diabetes was 7.0 years and initial HbA1c mean was 9.5% ± 1.2. Initial mean HbA1c was 9.8% ± 1.3 in the group receiving single dose (Group I), and it was 1.5% ± 9.3% in the double-dose group (Group II). At the end of 12 weeks, improvements in HbA1c levels were observed 1.8% in Group I and 1.5% in Group II (P=0.6). Change in A1c levels in the next 12 weeks after cross-over, were −0.2% and −0.1% in Group 1 and Group 2 (P=0.6). While the initial daily insulin doses were 0.11/kg in both groups, at the end of the first twelve weeks it was 0.29 in the Group I, and 0.32 in the Group II (P=0.2). After crossover, daily insulin doses were 0.42 and 0.38 (P=0.3) respectively. Daily insulin dose was only about 10% higher in double-dose periods and was not statistically significant in pre and post crossover periods.

Conclusion
Reason for the difference in dose requirement may be due to comfortable and easily titration ability feature of double daily dose. According to the results obtained in this study, a single daily dose of insulin detemir has a similar effect at the same dose of twice daily when used as basal therapy with oral antidiabetics.

DOI: 10.1530/endoabs.32.P472
P473
Cardiovascular effects of treatment with Liraglutide in a population with type 2 diabetes
Marco Zavattaro1, Flavia Prodani1,2, Maria Grazia Mauri2, Loredana Pagano2, Marina Caputo2, Sara Belcastro2, Gabriele Allochis2 & Gianluca Aimarti2
1Department of Health Sciences, Novara, Italy; 2Department of Translational Medicine, Novara, Italy.

Introduction
Liraglutide, a human GLP-1 analogue, is a new option for the treatment of type 2 diabetes (DM2). The purpose of this study was to evaluate the effects of liraglutide on cardiovascular risk factors in daily clinical practice in a heterogeneous population with DM2.

Subjects and methods
Four visits were scheduled in a 1 year study (baseline, 4, 8 and 12 months). Patients with a HbA1c not on target (>7%) during an oral hypoglycemic treatment, or patients intolerant to metformin were recruited. Exclusion criteria were: the presence of kidney diseases on dialysis, lack of compliance or refusal to injective therapy. Changes in systolic (SBP) and diastolic blood pressure (DBP) and cardiovascular risk scores (Framingham and UKPDS algorithms) were evaluated.

Results
243 subjects (110 males; 133 females) were consecutively recruited (age, mean±s.d., 59.6±10.4 years; disease duration 8.3±7.0 years).

Both SBP (154.7±22.0 vs 143.5±23.6 mmHg, P<0.0001) and DBP (89.1±11.5 vs 84.4±10.7 mmHg, P<0.0001) decreased respect to baseline. Both reductions were independent of changes in glucose, HbA1c and anti-hypertensive drugs. Framingham risk score decreased at 12 months respect to baseline (30.2±17.9 vs 35.6±20.3%, P<0.0001). At the same time a reduction in the risk of coronary events (15.7±11.4 vs 20.7±15.2%, P<0.0001) and of fatal coronary events (10.9±9.5 vs 15.2±13.8%, P<0.0001) was recorded. Finally, also the risk of stroke (8.6±8.5 vs 12.0±15.3%, P<0.0001) and fatal stroke (1.4±1.5 vs 2.3±3.3%, P<0.0001) at 12 months decreased respect to baseline. During the 12 months of observation no cardiovascular accidents occurred.

Conclusion
Liraglutide is effective in reducing blood pressure and cardiovascular risk in patients with DM2 in a relatively short-time treatment.

DOI: 10.1530/endoabs.32.P473

P474
Therapeutic switch at discharge improves medium term metabolic control in patients with type 2 diabetes and high vascular risk
Francisco Javier Vilchez-Lopez, Maria Belen Ojeda-Schuldt, Isabel Mateo Gavira, Cristina Lopez-Tinoco, Pilar Roldan-Caballero & Manuel Aguilar-Diosdado
Endocrinology Department, University Hospital Puerta del Mar, Cadiz, Spain.

Objective
To evaluate the impact of therapy with GLP-1 analogues (liraglutide) on glycemic control and weight loss in patients with type 2 diabetes and poor metabolic control.

Methods
Cross-sectional study including patients with type 2 diabetes and high vascular risk. Demographic and clinical characteristics, laboratory parameters, and diabetes treatment at baseline and discharge were analyzed. We used a specific insulin protocol during admission, switched treatment at discharge in selected cases and evaluated the metabolic control evolution 3 months after discharge.

Results
126 patients were included (55.6% male, mean age 64.3 years and mean duration of diabetes 16.3 years). 63.5% had hypertension, 47.6% dyslipidemia and 19% were smokers. 7.1% had a history of stroke, 40.5% coronary heart disease and 36.5% peripheral arteriopathy. Most prevalent causes of admissions: 22.2% amputation, 17.5% coronary bypass, 15.9% valve surgery and 15.1% coronary heart disease. Prior to admission, 38.9% were treated with insulin, 30.2% with oral hypoglycemic agents (OHA) and 25.4% with combined therapy. At discharge, 45.2% remained their previous treatment, adjusted if necessary and 43.5% started insulin treatment (8.7% basal insulin plus OHA, 7.1% basal insulin, 11.9% biphasic insulins, and 15.9% basal-bolus regimen). Mean HbA1c at admission decreased from 8.9% (18.6% patients, <7%) to 7.49%, (44.2% patients <7%) (P<0.0001) 3 months after discharge, with no significant differences detected in the rest of variables analyzed.

Conclusions
Most hospitalized patients with type 2 diabetes presented with poor glycemic control and chronic complications. Insulin consensus protocol can improve glycemic control during hospitalization. Optimizing therapy at discharge improves medium term metabolic control.

DOI: 10.1530/endoabs.32.P474

P475
Impact on weight and glycemic control in patients with type 2 diabetes and obesity treated with liraglutide
Virginia Hernando, Cristobal Morales, Clara Garcia, Ignacio Fernandez, Isabel Serrano & Angel Sendon
University Hospital Virgen Macarena, Seville, Spain.

Background and objectives
Evaluate the impact of therapy with GLP-1 analogues (liraglutide) on glycemic control and weight in patients with type 2 diabetes and poor metabolic control.

Material and methods
We conducted a retrospective observational study analyzing 67 patients with type 2 diabetes mellitus and BMI >30 kg/m² over 6 months of treatment. We evaluated HbA1c and weight at 3 and 6 months, performing statistical analysis with SPSSv18 using the Student’s t-test for paired data.

Results
The mean age was 50.29±13.2 years, being women the 50.7% of them. The average weight at baseline was 173.03±104.26 kg, BMI 38.5±5.99 kg/m² and mean HbA1c 8.4±1.3%. Initially 35.8% used oral antidiabetic monotherapy, 34.3% dual therapy with OAD, 9% triple therapy and the 20.9% remaining were treated with OAD plus insulin. Mean HbA1c at 3 months was 6.7±1.099, and at 6 months was 6.5±1.2, evidencing a statistically significant and clinically relevant decrease of mean HbA1c at 3 months of 1.81% (P<0.0000) and at 6 months of 1.3% (P<0.0000). The average weight at 3 months was 99.2±15.48 kg and at 6 months of 94.18±15.48 kg. We observed a weight loss of 7.46±5.8 kg (P<0.0000) after 3 months. At 6 months, there was a weight reduction from baseline of 13.5±16.5 kg (P<0.0000). There were mild gastrointestinal secondary effects in six patients that entailed the abandonment of treatment in three cases.

Conclusions
A clinically relevant reduction of HbA1c and weight were observed. The association of liraglutide to conventional diabetes treatment in type 2 diabetic patients with obesity confers a benefit on glycemic control and weight loss.

DOI: 10.1530/endoabs.32.P475

P476
Short-term, temporary insulin degludec, an ultra-long-acting basal insulin, as compared with glargine on the glycemic control in Japanese patients with type 2 diabetes
Shizuka Kaneko, Yumiko Tahara, Yuichi Sato & Masao Tashima
Takatsuki Red Cross Hospital, Takatsuki, Osaka, Japan.

Introduction
Insulin degludec (IDeg) is a new-generation insulin that forms soluble multi-hexamers after s.c. injection, resulting in ultra-long duration of action.

Conclusions
Most hospitalized patients with type 2 diabetes were treated with IDeg during hospitalization. We compared IDeg and glargine on glycemic control. Both regimens were effective in improving glycemic control without severe hypoglycemia.

DOI: 10.1530/endoabs.32.P476
Objective
We investigated the efficacy of glycemic control and safety on Japanese patients with type 2 diabetes who treated temporarily with IDeg or glargine and achieved target glucose level.

Research design and methods
Ten Japanese subjects with type 2 diabetes (male/female: 8/2, Age; 59.8 ± 12.1 years, disease duration; 3.9 ± 4.2 years, HbA1c; 9.0 ± 2.4%, BMI; 26.7 ± 3.7, FPG; 179 ± 49 mg/dl, 2hPBG; 291 ± 123 mg/dl, FCPR; 2.3 ± 1.3 ng/ml) were treated with a short-term, 3-4 week course of IDeg to achieve a target 2hPBG of <140 mg/dl without oral medication in admission. They were initially treated with 4 unit of IDeg and titrated according to the treat-to-target protocol. Efficacy and safety of short-term IDeg therapy were retrospectively compared with conventional basal insulin glargine therapy. Glycemic control after withdrawal of IDeg or glargine was also followed up.

Results
FPG of IDeg-treated group decreased to <100 mg/dl in 8.8 ± 2.2 days and remained in a flat and stable range. Maximum dose of IDeg to achieve target blood glucose level was 23.0 ± 4.8 unit/day on average. Blood glucose levels of IDeg-withdrawn patients were kept without medication or with only oral antidiabetic drugs. Hypoglycemic episodes were observed 3 times in a patient treated with IDeg, which were due to inappropriate exercise before meal. Treat-to-target protocol of IDeg provided prompt and fine glycemic control. Body weight was decreased by 2 kg on average with temporary IDeg therapy.

Conclusion
Short-term, temporary basal insulin IDeg therapy improved glycemic control in Japanese patients with T2DM.

DOI: 10.1530/endoabs.32.P477

P478
Perioperative liraglutide therapy for orthopedic patients with T2DM
Shizuka Kaneko1, Naoko Katagiri1, Yumiko Tahara1, Yuichi Sato1, Masao Tashima1 & Kumiko Hamano2
1Takatsuki Red Cross Hospital, Takatsuki, Osaka, Japan; 2Kanto Rosai Hospital, Kawasaki, Kanagawa, Japan.

Introduction
Diabetic patients with limited exercise during orthopedic perioperative period tend to gain weight, and their glycemic control frequently deteriorates. However, temporary insulin therapy has a risk of hypoglycemia. To investigate the efficacy and safety of perioperative liraglutide therapy, we performed a retrospective case analysis.

Research design and methods
Twenty one Japanese patients with T2DM (male/female: 9/12, Age: 68.2 ± 14.7 years, HbA1c; 8.0 ± 1.2%, BMI; 26.3 ± 2.7, 179 ± 49 mg/dl) were initially treated with 0.3 mg of liraglutide and allowed to dose-titrate up to 0.9 mg/day before elective orthopedic operations, e.g. spine surgeries (9 cases), artificial knee joint replacement (9), bone fracture surgeries (2), and amputation surgery of toe necrosis (1). In case of hyperglycemia (blood glucose level is over 200 mg/dl) during operation, regular insulin was added. Change in body weight, fluctuation of glycemic level, and perioperative complications were analysed.

Results
After initiation of liraglutide therapy, the body weight decreased in 3.3 ± 2.0 kg before operation. Liraglutide therapy achieved good glycemic control throughout the perioperative period. One patient suffering painful knee osteoarthritis lost weight with preoperative liraglutide therapy, and eventually he avoided the knee operation because his knee pain disappeared. Two patients could not increase dose-titrate up to 0.9 mg because of nausea as a side effect. Additional regular insulin was not needed except for 5 patients who were prescribed only 4 unit of insulin during operation. Twenty out of 21 patients withdrew liraglutide therapy after operation and rehabilitation. Hypoglycemic episodes, retardation of wound healing, or other complications were not observed.

Conclusion
Liraglutide provides an effective and optional way to safely achieve good glycemic control in perioperative for orthopedic operations subjects with T2DM, especially those with limited exercise ability and those at risk of hypoglycemia. DOI: 10.1530/endoabs.32.P478

P479
Insulinator: a computer program to help in the insulin therapy
José Pérez Rodríguez, Cristóbal Morales Portillo, Virginia Hernando Jiménez, Manuel Malagón Cobos, Isabel Serrano Olmedo & Ángel Sendón Pérez
Endocrinology and Nutrition Clinical Unit, Virgen Macarena University Hospital, Sevilla, Spain.

Introduction and objectives
In clinical practice many professionals are involved in the diabetes treatment. To facilitate this work, we present a computer program, based in recommended guidelines, to improve the management of insulin therapy, called insulinator. We evaluated the correlation between these and clinical practice.

Materials and methods
Insulinator has been made so that using a number of variables (weight, HbA1c and glycemic control) offer an orientation on the insulin therapy dose. This program present several regimens (basal insulin, mixtures, and basal-bolus regimen). You can start insulin, adjust the same regimen and increase to superior regimen. From 250 clinical histories, we compared the regimen and total dose introduced by endocrinologists in clinical practice, with virtually provide this software tool. The main variable is the concordance between both, considered as such an approximation of ± 15% of the total dose of insulin.

Results
Adjustment of the same regimen: C (concordance) L (lower dose) H (higher dose).
1 Basal insulin (29): C 93.10%, L 3.45%, H 3.45%.
2 Basal-bolus therapy (43): C 90.70%, L 4.65%, H 4.65%.
3 Basal insulin to basal-bolus regimen (20): C 80.00%, L 5.00%, H 15.00%.
4 Mixtures to basal-Bolus regimen (62): C 79.03%, L 9.84%, H 11.29%.

Conclusions
Insulinator is a useful tool in insulin management, showing concordance with useful clinical practice. We appreciate that the adjustment presents a very high concordance. However in the intensification this concordance is less, because it tends to underestimated the final dose of insulin. This has been intentionally in this direction to reach the same point but more prudently. Finally will be the professional who, based on calculations recommended by the program and considering the individual patient factors choose the final dose and insulin regimen.

DOI: 10.1530/endoabs.32.P479
P480
The long term effect of metformin plus DPP-4 inhibitor switching from metformin plus pioglitazone combination therapy in type 2 diabetes
Yonghyun Kim & Donghyun Shin
Endocrinology Division, Internal Medicine, Bundang Jesaeng Hospital, Seongnam, Republic of Korea.

Two years ago, we presented the short term 6 month results of metformin plus DPP-4 inhibitor combination therapy when we can’t reach the target below 7% of HbA1c with metformin plus pioglitazone combination that is best in terms of relieving insulin resistance in early diabetes.

Switching the pioglitazone to the DPP-4 inhibitor that improves insulin secretory dysfunction can be the next useful step to attain glucose control goal and DPP-4 inhibitors that increase insulin secretion by glucose dependent manner can also relieve insulin resistance because they improve first phase insulin secretion defect and prevent late hyperinsulinemia. DPP-4 inhibitor is also better than pioglitazone in weight aspect.

Total 111 patients were followed by 26.5 month (±9.7) after switching from metformin plus pioglitazone.

Sulfonylurea or pioglitazone was added for adequate glucose control in 14% (15/111) and the dose of DPP-4 inhibitor was decreased in 6% (7/111). The mean increasing dose of metformin to maintain HgA1c target who maintained metformin plus first dose of DPP-4 inhibitor in 80% (89/111) was 260 mg in the end.

HgA1c was improved in 76% (88 of 9) who maintained metformin plus first dose of DPP-4 inhibitor from 7.40 to 6.66% and the metformin dose was increased by 240 mg. HgA1c was aggravated in 22% (20/90) from 6.83 to 7.22%.

HOMA-IR was improved in 46% (0.91 ± 0.92) and aggravated in 53% (± 1.25 ± 1.17). Mean HOMA-IR change was −0.24 ± 1.51.

Mena weight reduction was 2.23 kg (± 3.17). The weight was decreased in 72% (3.63 ± 2.51) and increased in 19% (1.77 ± 1.73).

Although dose of metformin was slightly increased to maintain glucose control target with time, metformin plus DPP-4 inhibitor can be a good treatment option in maintaining insulin resistance as well as glucose and weight control as compared to Metformin plus pioglitazone therapy.

DOI: 10.1530/endoabs.32.P480

P481
Protective effects of Swietenia macrophylla King (seed & endocarp)- aqueous-methanolic extract on pancreatic islet histology in streptozotocin-induced diabetic rats
Hanan Kumar Gopalan, Nur Hayati Jafaar Marican, Rahim Mhd Noah & Rohani Mat Jais
UNIKL Institute Medical Science Technology, Kajang, Malaysia.

The oral antidiabetic drug, glibenclamide, stimulates the insulin producing β-cells constantly through a harsh mechanism which eventually may permanently reverse its endocrinofunction. The study investigates the protective effects from Swietenia seed and endocarp aqueous-methanol extract on pancreatic islets histology in rats of type 2 DM model. Phytochemical analyses were performed prior to the in vivo study to screen the aqueous-methanol extract of the combined plant parts. The experimental groups were rendered diabetic by chemical combination of STZ (65 mg/kg bwt, i.v.) and NAD (230 mg/kg bwt, i.p.) in adult rats. Diabetic rats were orally force-fed with glibenclamide (5 mg/kg bwt) or extracts (250 mg/kg bwt) daily for 3 weeks. Body weight (g) and FBG were measured i.p.) in adult rats. Diabetic rats were orally force-fed with glibenclamide (5 mg/kg bwt) or extracts (250 mg/kg bwt) daily for 3 weeks. Body weight (g) and FBG were measured

The oral antidiabetic drug, glibenclamide, stimulates the insulin producing β-cells constantly through a harsh mechanism which eventually may permanently reverse its endocrinofunction. The study investigates the protective effects from Swietenia seed and endocarp aqueous-methanol extract on pancreatic islets histology in rats of type 2 DM model. Phytochemical analyses were performed prior to the in vivo study to screen the aqueous-methanol extract of the combined plant parts. The experimental groups were rendered diabetic by chemical combination of STZ (65 mg/kg bwt, i.v.) and NAD (230 mg/kg bwt, i.p.) in adult rats. Diabetic rats were orally force-fed with glibenclamide (5 mg/kg bwt) or extracts (250 mg/kg bwt) daily for 3 weeks. Body weight (g) and FBG were measured i.p.) in adult rats. Diabetic rats were orally force-fed with glibenclamide (5 mg/kg bwt) or extracts (250 mg/kg bwt) daily for 3 weeks. Body weight (g) and FBG were measured

P482
Are there gender differences in liraglutide response in adults with type 2 diabetes?
Julia Sastre, Almudena Vicente, Esther Maqueda, Ines Luque, Enrique Castro, Amparo Marco, Virginia Peña & Jose López
Endocrinology, Complejo Hospitalario de Toledo, Toledo. Castilla-La Mancha, Spain.

Background
Recent reports suggest that female sex could be an indicator of better response to liraglutide in patients included in clinical trials.

Aim
To compare efficacy of liraglutide in women and men with type 2 diabetes mellitus (T2DM), in real clinical practice.

Patients and methods
Our study included 116 patients with T2DM and obesity (BMI >30) attending outpatient clinic, which initiated with liraglutide (0.6 mg/daily for the first week, followed by a dose of 1.2 mg/daily) and were studied prospectively during 6 months. Demographic, clinical and biochemical characteristics were collected at baseline and after 6 months. The percentage of patients achieving HbA1c <7% with no weight gain was assessed (responders). Data are expressed as mean (±s.d.) or as percentage.

Results
There were 49.1% men. At baseline the 2 groups were similar in age, years of evolution of DM, glycemic control and weight. At 6 months women and men showed significant reductions in weight and HbA1c from baseline (women: IMC 41.9 (8.6) vs 39.6 (7.2), P <0.001. HbA1c 7.8 (4.4) vs 6.8 (1.1), P <0.001). Men: IMC 37.4 (6.3) vs 36.0 (5.9), P <0.001. HbA1c 8.0 (1.3) vs 6.8 (1.1), P <0.001). There were no differences in the improvement of glycemic control between sex groups. The reductions in body weight were slightly greater in women but the difference was not statistically significant with men. There were more ‘responders’ between women but not statistically different (47.1 vs 62.9%, P: 0.187). Significant reductions in lipid and blood pressure occurred from baseline, but differences between the 2 groups were non-significant. No major hypoglycemia and a low incidence of minor hypoglycemia were seen in both groups.

Conclusions
This study demonstrates that liraglutide, in a real world setting, is associated with reduction in HbA1c, body weight, blood pressure and lipids in both sex groups. We did not find differences in liraglutide response between women and men.

DOI: 10.1530/endoabs.32.P482

P483
Degree of glycemic control in treated type 2 diabetic patients who live in a district of Madrid, Spain
Francisco Javier del Cañizo-Gomez, Manuela Belen Silveira-Rodriguez, Carlos de Gorgos Perez-Jauregui, Inmaculada Moreno-Ruiz, Tomas Gonzalez-Losada & Amparo Segura-Galindo
Hospital Universitario Infanta Leonor, Madrid, Spain.

Aim
To compare efficacy of liraglutide in women and men with type 2 diabetes mellitus (T2DM) in a district of Madrid, Spain.

Methods
Cross-sectional study in 501 consecutive patients with T2DM who attended regularly our outpatient clinic of Endocrinology in Madrid, Spain for a routine follow-up visits. In addition to routine ingredients glicated haemoglobin (HbA1c) and fasting plasma glucose (FPG) were measured in all of the subjects after and overnight fast. Only 353 of 501 patients were self-monitoring capillary glucose by home reflectance meters. The postranddual capillary glucose (PCG) was the mean of the last postbreakfast, postlunch and postdinner capillary determinations. On the basis of recommendations for adults with T2DM from the ADA, we applied the following goals for our comparisons: HbA1c <7.0%, FPG <7.2 mmol/l and PCG <10.0 mmol/l.

Results
Mean (±s.d.) age was 65.4 ± 11.9 years, 218 (44%) were male. Ninety-six (19%) met coronary artery disease (CAD). Overall, 56% patients received insulin therapy alone or both insulin and oral hypoglycaemic drugs (OHD), and the remaining 44% took taking OHD alone. Only 41% of patients meet the recommended ADA target of HbA1c <7%, the percentage was higher among subjects taking OHD than in those on insulin (48 vs 30%; P =0.007), whereas no
significant difference for HbA1c was found between individuals with and without CAD. More patients reached the target for PCG than for FPG (65 vs 27%) and there were no differences between the treatment subgroups.

Conclusion
The poor glycemic control observed in the diabetic population studied, supports the need for more aggressive treatment in these patients to achieve the goals recommended by the accepted guidelines.

DOI: 10.1530/endoabs.32.P483

P484
Copeptin: may it be a novel biomarker for insulin therapy in subjects with diabetes?
Ece Harman1, Yavuz Dodurga2, Gulsaç Gundogdu3, Ceylan Ayada4, Gülsen Eren5, Vural Kucukatay6 & Osman Genc4
1Department of Endocrinology, Ataturk Training and Research Hospital, Izmir, Turkey; 2Department of Physiology, Pamukkale University School of Medicine, Denizli, Turkey; 3Department of Physiology, Pamukkale University School of Medicine, Denizli, Turkey; 4Department of Physiology, Dumlupinar University School of Medicine, Kutahya, Turkey; 5Department of Physiology, Balikesir University School of Medicine, Balikesir, Turkey; 6Department of Medical Biology, Ege University School of Medicine, Izmir, Turkey.

Background and aim
As a prognostic marker, copeptin levels were independent predictors of survival in critically ill patients suffering from hemorrhagic and septic shock. Copeptin levels also have prognostic implications in chronic diseases other than acute illness. The stress-mediated activation of the HPA axis may be have role in the pathogenesis of the insulin resistance, metabolic syndrome, and diabetes. Furthermore, AVP action has been linked to liver glycogenolysis and insulin and glucagon secretion. We tested the hypothesis that plasma copeptin would be associated with stress, diabetes, and treatment of diabetes.

Materials and methods
Healthy male Wistar rats, about 3 months old, weighing 200–250 g, were obtained from University Animal House. They were housed in small cages at standard conditions (24±2 °C and 50±5% humidity) with a 12 h light:12 h darkness cycle and were fed ad libitum with standard rat chow and tap water. Rats were divided into four groups: eight control (C), eight diabetic (D), eight diabetic + insulin (DI) and eight stress (S) rats. Blood samples were collected into plain tubes (1.5 ml) and serum was separated via centrifugation at 1500 r.p.m. for 15 min. Samples were stored at −86 °C until analysis. Quantitative measurement of copeptin was performed using the ELISA method (Uscn Life Sciences, USA), according to the manufacturer’s instructions.

Results
There was not significant difference in terms of serum copeptin levels among groups except diabetes + insulin group.

Conclusions
Copeptin may be considered as a new tool for the comparison of the efficiencies of new therapeutic modalities in diabetes.

Figure 1 ELISA results of copeptin. C, control; S, stress; DM, diabetes mellitus; DM+I, diabetes mellitus + insulin; *P<0.05.

DOI: 10.1530/endoabs.32.P484

P485
Efficacy and safety of liraglutide in morbid obese patients in first year of commercialization in Spain
Immaculada Gonzalez- Molero, Rosario Vallejo, Marta Dominguez & Juan García-Arnés
Carlos Haya Hospital, Endocrinology Service, Malaga, Spain.

Aim
To evaluate the efficacy and safety for first patients treated in our clinic with liraglutide.

Methods
Retrospective study of patients who started treatment with liraglutide in the last year in our department. We collected data on age, years of evolution, chronic complications, previous treatment, physical examination, analytical parameters and side effects.

Results
Fifty-four patients. Follow-up: 4–12 months. Mean age: 53.8 (s.d. 11.9) years, 44.8% men. Pretreatment: 37% insulin and OADs, 48.1% only OADs and 14.8% without treatment. There were significant differences between initial and final weight 116.5 (s.d. 34.12) vs 110.94 (s.d. 27.9) kg (P = 0.007), mean blood glucose 150.81 (s.d. 56.49) vs 117.0 (s.d. 49.02) mg/dl (P = 0.006), HbA1c: 7.24 (s.d. 1.67) vs 6.35 (s.d. 1.22)% (P = 0.00), uric acid 5.93 (s.d. 1.66) vs 5.24 (s.d. 1.44) mg/dl (P = 0.04), C Peptide: 2.88 (s.d. 1.10) vs 5.52 (s.d. 3.69) (P = 0.04) and waist circumference 131.57 (s.d. 30.44) vs 124.14 (s.d. 21.48) cm (P = 0.05). There were no differences in systolic or diastolic BP, LDL-c, HDL-c, TG, TG/HDL-C, creatinine, microalbuminuria, liver enzymes, TSH or calcitonin. The average weight loss was 5.62 (s.d. 6.86) kg, significantly higher in men than in women (8.03±6.96 vs 0.65±2.27, P = 0.007), and correlated negatively with age (0.05) and positively with weight at the beginning (0.00). The mean decrease in HbA1c was 0.88±0.77 and correlated positively with baseline HbA1c (0.001). There was no correlation between the decrease in HbA1c and weight loss (0.31). Side effects: 4 patients reported nausea or postprandial discomfort in that in 1 case led to suspension. No hypoglycemia or other side effects occurred.

Conclusion
i) Liraglutide treatment in obese patients with T2DM achieve an effective reduction of weight, waist circumference and HbA1c, with scarce sides effects.

ii) Patients who might benefit more from this treatment would be men with higher HbA1c and weight.

DOI: 10.1530/endoabs.32.P485

P486
Evaluation of adolescents with type 1 diabetes after transition from paediatric to adult care
Marta Dominguez-López, Inmaculada González-Molero, Juan Pedro López-Sigüero, MSoledad Ruiz de Adana Navas & Federico Soriguer Escofet
Carlos Haya Hospital, Malaga, Spain.

Objective
Our objective in this study was to identify the type of clinical care received by young type 1 diabetic patients who have made the transition from paediatric to adult care, and to assess the metabolic status of the patients. The research aimed to develop a sustainable and coordinated approach to facilitating the transition between diabetes services for adolescents and reveal from the perspective of the adolescents living with type 1 diabetes their experiences surrounding the process of transition.

Material and methods
We evaluate all the patients transferred to our adult unit during the last year. Twenty-three type 1 diabetic patients were analysed. A questionnaire was used to evaluate the opinion of the patients concerning the transitional process.

Results
Twenty-three type 1 diabetic patients (63% F/36% M) with mean evolution of diabetes 9.5 years (6–14 years). Mean BMI was 23.68 kg/m², having 44.4% of the patients BMI higher than 25 kg/m². Mean HbA1c was 7.58% (6.5–8.6%). The patients were treated with MDI (18.18% with NPH and rapid insulin and 81.8% with premixed insulin). Nine percent had incipient nephropathy. No other chronic complications were found. The patients were quite satisfied with the transitional process.

Conclusions
Transition marks a critical phase for young, diabetic patients as they may frequently switch from one physician or centre to another. The individual optimization of therapy, established during paediatric care, provides the decisive
groundwork for disease control in young adults. It’s important to prepare, coordinate and evaluate transitional processes between paediatric and adult units.

DOI: 10.1530/endoabs.32.P486

P487
Insulin pump therapy as an obligatory treatment modality in a type 2 diabetic patient
Merve Yilmaz, Arzu Gedik, Tevfik Demir, Mehmet Calan, Tugba Gümüş, Ulku Aybükü Tunc, Abdurrahman Çömlekci, Serkan Yener, Sevinc Eraslan & Firat Bayraktar
Endocrinology Department, Medical Faculty, Dokuz Eylül University, Izmir, Turkey.

Introduction
Continuous s.c. insulin infusion (CSII) therapy is a well documented treatment modality in type 1 diabetes mellitus (DM), but its usage in type 2 DM has not become prevalent so far. It may be a treatment alternative in severely insulin resistant type 2 diabetics receiving high doses of insulin. We present a type 2 diabetic patient that we had to shift from multiple dosage insulin (MDI) injection to CSII therapy due to the widespread echinosis at the insulin injection sites.

Case
Fifty-seven-year-old female patient with type 2 diabetes for 19 years was on insulin therapy for 6 years of the last four being as MDI therapy. She describe decchymosis at insulin injection sites from the onset of insulin therapy. Her hematological tests for coagulopathy were completely normal. Due to the injection site problems her glycemic control could not be achieved (frequent hypoglycemic and hyperglycemic episodes) with MDI after which switch to CSII therapy was done. Her compliance to CSII was well and she didn’t experience large glucose fluctuations during with this therapy anymore. After initiation of CSII, her daily insulin need decreased and HbA1c improved markedly (Table).

Table 1: HbA1c and total daily insulin need before and after CSII

<table>
<thead>
<tr>
<th></th>
<th>Pre-CSII</th>
<th>Post-CSII (3rd month)</th>
<th>Post-CSII (6th month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>7.2</td>
<td>6.4</td>
<td>6.1</td>
</tr>
<tr>
<td>Meandalyinsul-(uni-ts/day)</td>
<td>54</td>
<td>32.4</td>
<td>32.4</td>
</tr>
</tbody>
</table>

Conclusion
Studies about CSII therapy in type 2 DM have demonstrated that this therapy improves the glycemic control, decreases the insulin need and HbA1c of the patients. In addition less blood glucose fluctuations and better quality of life measures were recorded with this treatment modality. Insulin administration with CSII seems to be an alternative in selected type 2 diabetics as in our case.

DOI: 10.1530/endoabs.32.P487

P488
Absence od metformin therapy and inadequate insulin doses are the basic features of diabetic patients with unregulated diabetes
Dragan Tesic, Milena Mitrovic, Damir Bene & Djordje Popovic
Clinic of Endocrinology, Diabetes and Metabolic Disorders, Novi Sad, Serbia.

Introduction and objectives
The aim of our study was to determine which characteristics of the uncontrolled diabetes are among randomly selected patients with type 1 (T1DM) and type 2 (T2DM) diabetes.

Material and methods
A total of 194 diabetic patients were observed, 142 with T2DM and 52 with T1DM, recruited in outpatient clinic. Patients were divided into three groups according to HbA1c values: <7% (G1), 7–8% (G2) and >8% (G3). Statistical analysis: t-test, test of proportions, multiple logistic regression analysis.

Results
Patients (G1–G3) did not differ by age, prevalence of types 1 and 2 diabetes: T1DM (59.6%; 25%; 15.4%) and T2DM (55.3%; 23.3%; 21.3%) and disease duration. G1 compared to the G3 significantly differ or with the tendency of significance in representation of males (38.6 vs 56.3%, P=0.02), triglyceridemia level (1.8±1.4 vs 1.4±0.9 mmol/l, P=0.10), fibrinogen (3.7±0.8 vs 3.4±0.8 g/l, P=0.05) and platelets (259.3±60.5 vs 230.1±60.7*10^9/l, P=0.02) were lower (165.5±10.3 vs 169.5±10.9 cm, P=0.06), with less the used biguanides (45.6 vs 65.6%, P=0.07) and especially sulphonylurea (23.7 vs 46.9%, 0.02), and more were on insulin therapy (84.2 vs 53.1%, P<0.01), with multiple daily insulin dose (49.2 vs 37±12, P=0.01) and more frequent retinopathy (57.1 vs 56.7%, P=0.07). G1 to G2 patients were more often on insulin therapy (81.3 vs 53.1%, P=0.01).

Conclusions
Patients with glucose unregulation were characterized with clusters of components that are the part of increased insulin resistance (increased insulin dose…) and with simultaneous therapeutic inconsistency to it (metformin therapy). As a consequence, there were increased level of hemostatic components (platelets, fibrinogen) and increased incidence of diabetic retinopathy.

DOI: 10.1530/endoabs.32.P488

P489
Analysis of the newly diagnosed diabetic patients, one year and five years of evolution, C-peptide, autoimmunity, treatment and metabolic control
Marta Domínguez-López, David Fernandez-Arias, Inmaculada González-Molero, Natalia Colombo, Marisol Ruiz de Adana & Federico Soriguer
Endocrinology Department, Carlos Haya Hospital, Málaga, Spain.

Objective
We retrospectively analyzed patients with type 1 diabetes onset, attended during the years 2005 and 2006 on the specific query of type 1 DM debut of a tertiary hospital, with initial treatment assessment, at 1 and 5 years evolution.

Results
Patients were treated for newly diagnosed DM 1, 25 patients (72% male, 28% female) mean age 23.2 years (14–36), mean BMI: 23.18 (18–33.8%). The clinical presentation included: 88.24% presented with weight loss average (mean: 8.91 kg (4–18 kg), 28% of patients had ketoacidosis requiring hospitalization 41% (mean stay: 5.7 days). In 65% of patients starting insulin therapy was prescribed in endocrinology. Of the patients who weren’t initially treated in our Endocrinology Department 40% were treated with NPH, 20% with mixed insulin (rapid analogs and NPH) and 40% with OHA (oral hypoglicemic agents). The initial insulin therapy regimens used in our clinic were: 5% 2 doses of NPH, 38.8% 3 mixed insulin (NPH and rapid analog in three doses). 55.54% of patients initiated functional basal-bolus insulin therapy (Lantus/Levemir + rapid analogues).

At baseline, mean HbA1c: 10.58%, mean C-peptide: 1.1. Autoimmunity to GAD positive in 80%, 52% for IA2 and 23.8% for antiinsulin antibody.

After a year of evolution, 81.25% of patients have a functional basal-bolus insulin therapy, with a mean insulin requirements 0.49 U/kg per day, mean HbA1c 6.4%, average Peptide C: 1.0, Autoimmunity positive for GAD 79% for IA2 50% and 45.8% for anti-insulin Ab.

After 5 years of evolution, 100% of patients have a functional basal-bolus insulin therapy, with mean insulin requirements 0.75 U/kg per day, mean HbA1c 7.2%, with a mean weight gain of 1.9 kg and counting carbohydrate portions of up to 67% of cases.

Conclusions
In endocrinology tends to precocious intensive insulin therapy since DM1 debut, with an exponential increase in the usage of insulin analogues to mimic as much as possible the physiology of the pancreas. But there is a percentage that optimal treatment is delayed for late referral to the Endocrinology Department, mainly from primary care.

DOI: 10.1530/endoabs.32.P489

P490
Assessment of diabetes knowledge evaluation in type 2 diabetic patients
Inmaculada González-Molero, Marta Domínguez, MArisol Ruiz de Adana & Federico Soriguer
Carlos Haya Hospital, Endocrinology Service, Málaga, Spain.

Introduction
Research has demonstrated that knowledge about medications, diet, exercise, home glucose monitoring, foot care, and treatment modifications is necessary to effectively self-manage diabetes, and the assessment of diabetes-related
knowledge is an important first step from which to individualize diabetes education programs and make evaluations of their effectiveness.

Purpose
To assess the knowledge of diabetes mellitus (about the disease, its risk factors, signs/symptoms, related complications and suitable diet and lifestyle) among our type 2 diabetic patients and to identify knowledge deficits and patient specific features that are associated with this knowledge.

Material and methods
A cross-sectional sample survey of patients’ knowledge of diabetes was carried out by administering a 23-item diabetes knowledge questionnaire adapted to Spanish language to collect information. A total of 90 type 2 diabetic patients, mean age 62.1 (11.7 s.d.) attending our clinic during 4 months were interviewed. We collected data about age, sex, time of evaluation, chronic complications, treatment, cardiovascular risk factors, comorbidities, anthropometric (weight, BMI, waist perimeter) and analytic parameters.

Results
Ninety patients were evaluated, mean age 62.1 ± 11.7 years, 57.1% men. Mean duration of the diabetes was 12.2 ± 8.66 years, with mean time of attendance in our Endocrinology Department 3.45 ± 3.47 years. 35.7% presented chronic complications disease-related; HbA1c was present in 70% of the patients, obesity in 73% and dyslipemia in 83.3%. Thirty percent of the patients were treated with oral hypoglycemic agents (OHA), 10% were insulin treated and 60% with combined treatment (insulin plus OHA). Mean BMI was 33.8 ± 4.8, and mean HbA1c 7.55 ± 1.05%. 51.9% of the patients answered correctly more than 75% of the questions and 48.1% of the patients more than 50%. None of the patients answered correctly <50%. The number of right answers was statistically significant regarding age (mean 58.2 ± 12.9 years in more than 75% of right answers vs 65.1 ± 10.1 years in 50–75% of right answers, P = 0.05), but there were no significant differences depending on years of evolution (12.7 ± 10.2 vs 10.3 ± 6.3), BMI (33.5 ± 5.5 vs 33.7 ± 4.9), HbA1c (7.4 ± 1.2 vs 7.8 ± 0.7%) or time of endocrinology clinic attendance (4 ± 4.1 vs 2.7 ± 2.5 years). There were also no statistically significant differences depending on sex, chronic complications or previous educational programs. Insulin treated patients answered correctly more questions (more than 75% of right questions) than patients treated with OHA (100% in insulin treated patients vs 41.2% in patients treated with OHA, P = 0.026).

Conclusions
In our group of DM2 patients, we can conclude that most of them had appropriate diabetes related Knowledge. Patients with better scores had less mean age, and were treated with insulin. Priority needs to be given by education programmes to give patients a better knowledge of their disease, to prevent premature morbidity and mortality associated with diabetes.

DOI: 10.1530/endoabs.32.P490

P492
Hypoglycemic evaluation of Swietenia macrophylla King combined seed and endocarp extracts: a comparative study between hot water extraction and aqueous-methanol extraction
Rahim Mhd Noah, Nur Hayati Marican Jaafar, Hanan Kumar Gopalan & Mohamad Rohani Jais
UNIKL Institute of Medical Science, Kajang, Malaysia.

Solvent and process variables were critical to optimize the extractions of potential hypoglycemic compounds within medicinal plants. Hence, the undertaken study was designed to evaluate the hypoglycemic effectiveness exhibited by extraction performed in decoction manner using water as solvent and compares it with an aqueous-methanol solvent extraction. To evaluate the extractions prepared, phytochemical assays and in vivo study in induced-diabetic rats were carried out.

Results indicates aqueous-methanol extract as active for alkaldoids, flavonoids, cardiac glycosides, reducing sugar, saponins, tannis and terpenoids. It is also more efficient than the hot water extract in improving altered biological parameters impacted by hyperglycemia. As such, aqueous-methanol appears ideal for extracting the necessary potent hypoglycemic compounds within the plant parts studied.

Key Words: S. macrophylla King, Hot Water Extract, Aqueous-Methanol Extract, Hypoglycemic.

DOI: 10.1530/endoabs.32.P492

P491
Advantages of using DPP-4 inhibitors in patients with type 2 diabetes mellitus and overweight
José Pérez Rodríguez, Cristóbal Morales Portillo, Ignacio Fernández Peña, Isabel Serrano Olmedo, Maria del Carmen De la Cuesta Mayor & Angel Sendrón Pérez
Endocrinology and Nutrition Clinical Unit, Virgen Macarena University Hospital, Sevilla, Spain.

Objective
Analyze the use of DPP-4 inhibitors (iDPP4) in a specialized consultation as well as metabolic impact, weight and safety in patients with diabetes mellitus type 2 (DM2).

Material and methods
We analyzed 100 patients with DM2, derivative to Diabetes hospital with debut or poor glycemc control. We initiated them sitagliptin 100 mg/day and reinforced Diabetes education. We studied the HbA1c, weight and severe hypoglycemia. Statistical analysis was performed with SPSSv18, making a t-student and Wilconson test.

Results
Forty-six percent of our patients were referred in debut and the remaining 64% with DM2 poorly controlled. They had a mean age of 57.6 ± 12.7 years and a mean of 4.8 ± 6.4 years of DM2 evolution and had a mean BMI of 30.5 ± 4.9 kg/m². We appreciated a total decrease of mean HbA1c of 9.2 to 6.6% (-2.7±%) and a total mean weight loss of -1.57 kg. In none of the patients observed severe hypoglycemia. Besides the subgroup analyzed by combined use with sitagliptin.

– Monotherapy (n = 3): decrease mean HbA1c from 7.3 to 6.1% (-1.2%), and average weight loss of -2.80 kg.*
– Dual therapy (n = 55): decrease mean HbA1c from 9.4 to 6.4% (-3.0%), and average weight loss of -2.97 kg*.
– Triple therapy (n = 7): decrease mean HbA1c from 8.1 to 6.9% (-1.2%), and average weight loss of -3.09 kg*.
– Insulin basal therapy (n = 35): decrease mean HbA1c from 9.4 to 6.6% (-2.8%), and average weight loss of -0.75 kg*.

*P < 0.05

Conclusions
The most frequent use of iDPP4 was performed in combination therapy with metformin, followed by association with basal insulin plus metformin. Therapy with DPP-4 is effective treatment option in the first step (in intolerant to metformin), as 2nd oral drug, in triple therapy, even with basal insulin. The profile beneficial weight and hypoglycemia security makes it ideal for the treatment of overweight patients with DM2.

DOI: 10.1530/endoabs.32.P491

P493
Evaluation of BICI therapy in pregestational type 1 diabetes
Pilar Roldan, Isabel Mateo, Jose Ortego, Gloria Baena, Laura Larran, Inmaculada Gavilan, Belen Ojeda, Julian Tamayo & Manuel Aguilar-Diosdado
H.U. Puerta Del Mar, Cadiz, Spain.

Objective
To evaluate in our area BICI therapy efficacy in pregestational type 1 diabetes.

Methods
We conducted a descriptive retrospective analysis studying metabolic control and obstetric results in patients with pregestational type 1 diabetes, treated with BICI between 2004 and 2012 in our hospital.

Results
We evaluated 28 patients with type 1 diabetes and diabetes duration of 17.3 ± 6.6 years. In 27.3% of patients the treatment with BICI was indicated for reasons other than pregnancy. Of the remaining, 18.7% performed treatment with BICI planning pregnancy, and in 81.3% started this therapy for bad metabolic control during the pregnancy, despite intensive insulin therapy. Only 39.3% of pregnancies were planned. Women had no ketoacidosis or severe hypoglycemia. Regarding the onset and progression of chronic complications, only in one patient was detected progression of diabetic retinopathy. The completion of gestation was 34.2 ± 5.4 weeks and was performed by planned cesarean in 28.6%, urgent cesarean in 25% and vaginal delivery in 14.3% of the cases. Two patients had spontaneous abortion. There were no others perinatal complications, presenting fetal macromasia 31.25% of newborns.

Conclusions
BICI therapy represents a safe and effective strategy to optimize metabolic control in patients with pregestational type 1 diabetes poorly controlled with
conventional intensive insulin treatment, to plan pregnancy or to achieve good metabolic control in the case of unplanned pregnancies.
DOI: 10.1530/endoabs.32.P493

P494
Quality indicator of glycemic status in patients with diabetes mellitus in primary health care in the Kyrgyz Republic
Elmirgul Omorova
Kyrgyz State Medical Institute of Post-Graduating Training and Continuous Education, Bishkek, Kyrgyzstan.

Introduction
Basic medical care to patients with diabetes mellitus (DM) in Kyrgyzstan is on the primary care level, in family medicine centers.

Methods
We have analyzed, in a random order histories of diseases of 928 outpatients observed and registered patients with diabetes in primary health care clinics, in Bishkek.

Results
The basic amount of patients were women 656 (70.7%), and men 272 (29.3%) respectively. The mean age was 63.8 (± 10.5) in range 29–89 years. Glycemic status of patients was determined by following tests: fasting glucose, glucose 2 h after eating, and glycated hemoglobin (HbA1c). Examination of blood glucose was performed in all patients of our study after getting informed consent. The result of our study showed the mean value of glucose 8.71 mmol/l (± 3.04), where we discovered 318 (34.3%) compensated patients vs 610 (65.7%) decompensated patients. Situation of blood glucose evaluation after a meal and HbA1c of patients with diabetes mellitus in Kyrgyzstan is in a poor condition, as primary care physicians do not pay enough attention to this analysis. In result of our investigation there were evaluated only 82 (8.84%) patients by blood glucose test with diabetes mellitus.

Conclusions
Thus, my results proved that the quality of primary care of diabetic patients in Kyrgyzstan requires improvement and perfection. It is recommended to introduce clear standards of diagnostic services.
DOI: 10.1530/endoabs.32.P494

P495
Pre-diabetes study in Libya: delay and prevention T2DM
Abduladim Ellobgi
Elkhidra Hospital, Tripoli, Libya.

T2DM is expected to rise to 552 million by 2030. DM is associated with complications which result in reduced quality of life and premature mortality. T2DM has a long asymptomatic pre-clinical phase (~5–10 years) which frequently goes undetected. Benefits of early diagnosis on outcomes in screen-detected DM remain unclear. Some indirect evidence suggesting that early detection and intervention may be beneficial. Screening for DM will identify individuals with intermediate hyperglycemia (IGT and IFG) who may benefit from interventions to prevent or delay DM and complications. Lifestyle changes can prevent or delay DM by up to 58% in people with prediabetes.

Libya has 6 million inhabitants with ~17% people with DM and about 24% if we add people with IFG in 2009. This is the first study in Libya screening for people with pre-diabetes.

Study aims: i) establishing screening program to prevent or delay DM, ii) identifying people at high risk of DM and with asymptomatic hyperglycemia, iii) encouraging people to have a risk assessment. Four thousand non-diabetic individuals in the capital city of Tripoli (2.2 million inhabitants), age 45 years and above with conditions that increase risk of DM will be included. Risk assessment questionnaire followed by diagnostic blood tests will be used. Venous blood tests will be offered to adult with high risk scores. If FBS <100 mg/dl or HbA1c of <6.0%, a brief intervention and weight loss program will be offered. High risk score and FBS of 100–126 mg/dl or HbA1c of 6.0–6.4%, information will be offered in their particular risk factors. People with possible T2DM, FBS of 126 mg/dl or above, or HbA1c of 6.5% or above, but no symptoms of T2DM, second blood test will be carried if type 2 diabetes is confirmed treatment will be offered.
DOI: 10.1530/endoabs.32.P495

P496
Molecular docking research analysis of novel natural and synthetic PTP 1B inhibitors as potential therapeutic target for diabetes mellitus
Danish Ahmed1, Manju Sharma2, Vikas Kumar1 & Pankaj Yadav Subhashchandra1
1Department of Pharmaceutical Sciences, Faculty of Health Sciences, Sam Higginbottom Institute of Agriculture, Technology and Sciences-Deemed University, Allahabad, India; 2Department of Pharmacology, Faculty of Pharmacy, Jamia Hamdard University, New Delhi, India.

Augmented pervasiveness of type 2 diabetes mellitus and obesity has amplified the medical necessitate for new agents to treat these disease states. Both type 2 diabetes and obesity are connected to the resistance to the hormones insulin and leptin. Protein tyrosine phosphatase 1B (PTP1B) has been shown to function as negative regulator of insulin signalling as well as leptin signal transduction. At present there are copious compounds synthesized as PTP1B inhibitors. The development of compound libraries with more selective PTP1B inhibitors has been bumped up by the realization that many natural products have PTP1B inhibitory activity and therefore are attention-grabbing biologically lead compounds. This research exertion shows the molecular docking analysis of novel synthetically prepared compounds and new-fangled isolated natural PTP 1B inhibitors as novel target for type 2 diabetes.

Figure 1 Negative Regulation of Insulin and Leptin Pathways by PTP 1B
DOI: 10.1530/endoabs.32.P496
Endocrine disruptors

P497

Reproductive aging in rats is altered by developmental exposure to mixtures of endocrine disrupters
Julie Boberg, Louise Krag Isling, Sofie Christiansen, Marta Axelstad, Pernille Jacobsen & Ulla Haas
Technical University of Denmark, National Food Institute, Søborg, Denmark.

Long-lasting and/or delayed reproductive effects of developmental exposure to mixtures of environmental chemicals were investigated in rats. Wistar rats were exposed to mixtures of estrogenic or anti-androgenic endocrine disrupters in pregnancy and lactation, and effects in offspring at 12–18 months of age were studied. The mixture included 13 estrogenic and anti-androgenic chemicals, including phthalates, pesticides, u.v.-filters, bisphenol A, butylparaben and paracetamol, and the mixture ratio was chosen to reflect high end human intakes. In the animal study, two groups received exposures of 150 and 450 times high end human intake levels of these chemicals combined, and one group received a mixture including only the anti-androgens.

Females exposed to the mixture showed earlier reproductive aging, and males had reduced epidydial sperm count, histological changes in the epidydium, and normal prostatic aging (atrophy) was altered towards hyperplasia. A possible increased incidence of pituitary adenomas in the mixture groups could be related to the altered age of reproductive senescence. These effects were mainly attributed to the anti-androgenic compounds in the mixture, as comparable effects were in most cases seen in animals exposed to the total mixture and in the group receiving a mixture of anti-androgens only. A previous publication describes endocrine disrupting in prepubertal offspring (Christiansen et al., Int J Androl 2012 35 (3) 303–316), and these early findings can be a signal of severe adverse effects later in life.

This study demonstrated that developmental exposure of rats to endocrine disrupters can induce long-lasting effects manifested in early reproductive senescence, and perinatal programming of the hypohalamo-pituitary-gonadal axis may account for the observed changes in the timing of aging-related events.

DOI: 10.1530/endoabs.32.P497

P498

An investigation about metabolic disruption: organostannic compounds as PPAR gamma agonists
Isabella Gontijo de Sá Leão, Angélica Amorim Amato, Natacha Thalita Santos Amorim, Lilic Teixeira Cortés & Francisco Assis Rocha Neves
Pharmacology Laboratory, Health Sciences Faculty, University of Brasília, Brasília, Brazil.

The parallel increase in the amount of environmental contaminants and in the prevalence of some human diseases has led to a growing interest in understanding how these compounds, so-called endocrine disruptors, may affect human health. In this scenario, the concept that obesity is the result of the interplay of genetic and lifestyle factors has been changing due to the growing evidence that environmental contaminants might alter endocrine function.

Organostannics are a distinct class of organic pollutants related to paints used in environmental contaminants might alter endocrine function. This effect appeared to be specific for PPARγ, since DBT, benzole TBT and also TBT had no activity on glucocorticoid, estrogen and thyroid hormone receptors when assessed by reporter gene assays using the respective expression vectors and responsive element-driven luciferase reporter.

Further studies are being carried out to investigate the effect of these compounds on cell based adipogenesis, PPARγ-responsive genes and also in vivo. Additionally, we seek to investigate their mode of binding to the binding pocket of PPARγ. These results may provide a better understanding of how these pollutants affect in human health and possibly the increasing rates of obesity and its associated diseases worldwide.

DOI: 10.1530/endoabs.32.P498

P499

Tributyltin changes the thyroid gland morphology of male rats
Paula Rodrigues Pereira, Romulo Medina de Mattos, Celia Yelimar Palmiero, Rodrigo Fortunato, Jones Bernardes Gracelli, Denise Pires de Carvalho, Luiz Evo Rico Nascimento & Leandro Miranda-Alves
1Universidade Federal do Rio de Janeiro, Rio de Janeiro/RJ, Brazil; 2Universidade Federal do Espírito Santo, Rio de Janeiro/RJ, Brazil.

Triorganotins, such as tributyltin (TBT), are environmental contaminants commonly found in antifouling paints that are used on the ships and other vessels. Unfortunately, these chemicals are also suspected to cause endocrine-disrupting effects in mammals, due in part to their possible transfer through marine food chains and to the consumption of contaminated seafood. The importance of triorganotins as environmental endocrine disruptors in different animal models is well known; however, the adverse effects on thyroid gland are less well understood. We evaluate the potential histophysiologys changes induced by TBT on the thyroid gland. Male Wistar rats (8 weeks old, 250 g) were divided into 3 groups: control, vehicle, 0.4% ethanol), TBT, (100 ng kg⁻¹ day⁻¹) and TBB, (200 ng kg⁻¹ day⁻¹) treated for 15 days by gavage. After the treatments, the animals were sacrificed and thyroid glands were fixed for histological analysis. TBT (both doses) promoted a disorganization of follicular cells, with hypertrophy and hyperplasia of thyrocytes, increase in number of mast cells, increase in collagen deposition and glandular congestion compared with control thyroid gland. However, we did not observe changes in plasma levels of T₃ and T₄ after 15 days of treatment. Also, we showed a significant decrease in cell viability with the doses of 2.0×10⁻¹ and 1.0×10⁻¹ ng/ml TBT for 2 and 3 h, using PCCL3 cells (in vitro model of thyrocytes).

In this work, we observed that TBT-exposure in thyroid gland induces morphological changes and may correspond to a potential risk factor for thyroid disorders in mammals.

DOI: 10.1530/endoabs.32.P499

P500

Sex hormone-induced gender differences in vascular muscle cells motility are susceptible to the environmental disruptors
Marco Pellegrini & Maria Marino
Section Biomedical Science and Technologies, Department of Science, University Roma TRE, Rome, Italy.

Sex steroid hormone-induced variations of vascular smooth muscle cells (VSMCs) migration are critical in determining the sex/gender-related differences in male and female pathophysiology of cardiovascular system. Although several substances present in the environment, defined endocrine disruptors (EDs), could interfere with androgen and estrogen effects, the sex/gender-related susceptibility of VSMC motility to these substances is completely unknown. Here, naringenin (Nar) and bisphenol A (BPA) effects on male and female VSMC motility has been evaluated. VSMC motility was determined by Wound healing and cell migration assays. 17β-estradiol (E₂, 1–10 nM) induced a dose-dependent inhibition of motility in female-derived VSMC. In contrast, neither testosterone nor dihydrotestosterone (0.01–100 nM) modified male-derived VSMC motility. E₂ subtype-dependent activation of p38 was necessary for the E₂ effect on cell motility. High BPA concentration prevented E₂ effects in female-derived cells being without any effect in male-derived cells. Nar mimicked E₂ effects on female-derived cells even in the presence of E₂ or BPA or in male-derived VSMC. This latter effect was blocked by ERB subtype inhibitor pre-treatment, but not by the AR inhibitor. These observations indicate that E₂ plays a pivotal role in the protection being the main receptor to mediate the effect of E₂ in the vascular wall. Moreover, although E₂ signals in VSMC are more susceptible to the impact of EDs than androgen signals, male-derived cells, expressing both ERs, possess a similar susceptibility to EDs than female-derived cells.

DOI: 10.1530/endoabs.32.P500
P501
Vitamin E protects against methomyl-induced reproductive toxicity in pregnant female rats
Mosbah Rachid1 & Yousef Mohktar Ibrahim2
1Department of Biology, Faculty of Sciences, University of Bournemouth, Bournemouth, Algeria; 2Department of Environmental Studies, Institute of Graduate Studies and Research, Alexandria University, 21526, Alexandria, Egypt.

Purpose
The aim of this study was to evaluate the effects of methomyl 25%WP (Lannate, carbamate broad spectrum insecticide) on the reproductive parameters in female Wistar rats during pregnancy and the possible protective role of vitamin E against methomyl-induced toxicity.

Methods
The animals were randomly divided into four groups, eight of each. Group I served as control; Group II received orally a dose of methomyl (Met, 10 mg/kg per day). Group III was dosed via gavage by vitamin E (Vit E, 100 mg/kg per day). Group IV received a concomitantly treatment of methomyl plus vitamin E (Met + Vit E). The treatment lasted from GD1 to GD15. Body weight gain, food and water intake, progesterone levels (at GD18) and pregnancy outcomes were evaluated, then after post-partum, dams were sacrificed, adrenal and ovary organs were excised, weighed and used for histological examinations.

Results
When compared with control, methomyl group showed a significant decrease in ovary relative weights, progesterone levels, litter size, sex ratio, gestation index and the newborn mean weight. In the other hand, the histological adrenal and ovary examination revealed pathohistological changes marked by cells disorganization and vacuolization in the adrenal gland, as well as degenerative changes with a few number of healthy follicles and many atretic follicles at different stages of development in ovary. In addition, Vit E group displays similar pregnancy outcomes and histological structure in both adrenal and ovary organs when compared with control, however a slight elevation in progesterone level was noted. The co-administration of Vit E along with methomyl reversed partially or completely all the adverse toxic effects generated by methomyl. In conclusion, it is clear that vitamin E has a potential protective role against methomyl-induced reprotoxicity in female treated during pregnancy and this may result from its antioxidant properties proven in several recent studies.

DOI: 10.1530/endoabs.32.P501

P502
Bisphenol-A modulates proliferation of human breast adenocarcinoma cells (MCF-7) by modulating apoptosis and cyclin-A
Tomas Havranek, Ladislav Macho & Maria Fickova
Institute of Experimental Endocrinology, Slovak Academy of Sciences, Bratislava, Slovakia.

Endocrine disruptors represent exogenous substances that alter hormonal, reproductive, immune and homeostatic systems. Bisphenol-A (BPA) in the form of polymer is a part of polycarbonates used in plastics, food packing and medical devices. Incomplete BPA polymerization and cleavage of weak chemical bonds result in monomer release/leakage to the foods and beverages. Many studies have associated exposure to BPA with higher incidence of hormone-dependent mammary and prostate carcinomas. In present study we investigated the effect of BPA on proliferation of MCF-7 cells in cell culture. Dose (1X10⁻²-1X10⁻⁵M) and time (24-120 h) dependent effects of BPA were compared with estradiol (E2) effects. Cell growth was measured by WST-1 test, de novo synthesis of DNA with BrdU incorporation to DNA, apoptotic proteins and cyclin-A were determined by Western blot. Compared to E2, high concentrations of BPA significantly stimulated cell growth after 48 h treatment. Long-term effect of BPA (96, 120 h) similarly stimulated cell proliferation (40%), however the impact did not achieve the effect of E2 (80-130%). Stimulatory effect of BPA on cell proliferation (48 h) was accompanied by huge increase (~2000%) of de novo DNA synthesis even after 24 h. At longer time expositions BPA effects significantly declined and were comparable with those of E2. BPA reduced expression of pro-apoptotic proteins p53 (48 h) and Bax (24 h) by dose dependent manner (vs E2), while expression of anti-apoptotic protein Bcl-2 was increased after 96 h only. BPA in low and high doses significantly reduced cyclin A protein expression as compared to E2. In conclusion, BPA effects on MCF-7 cells proliferation result from alteration of several cellular processes like synthesis DNA, disturbed synthesis/degradation of apoptotic proteins and proteins of cell cycle division and replication. Effects of BPA are dose-dependent. Supported by grants of VEGA 20107/10 and APVV 00147-10.

DOI: 10.1530/endoabs.32.P502

P503
Protective potential of 17-beta-estradiol on membrane linked functions in aging female rats: a behavioral, biochemical and ultrastructural study
Pardeep Kumar, R K Kale & N Z Baquer
Jawaharlal Nehru University, New Delhi, India.

Background
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 b-amyloid protein (Ab). These changes increase during menopausal condition in females when the level of estradiol is decreased.

Objective
The objective of this study was to investigate neuroprotective potential of 17b estradiol (E2) treatment on the activities of acetylcholinesterase and monoamine oxidase, membrane fluidity, neurolipofuscin, genomic DNA degradation, protein oxidation levels and testing learning memory, occurring in brains of female rats of 3 months (young), 12 months (adult) and 24 months (old) age groups, and to see whether these changes are restored to normal levels after exogenous administration of estradiol.

Methods
The aged rats (12 and 24 months old) (n=8 for each group) were given subcutaneous injection of 17b-estradiol (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. Learning was tested in a Morris water maze and ultrastructural studies of brain region by MRI.

Results
The results obtained in the present work revealed that normal aging was associated with significant increases in the activity of monoamine oxidase, genomic DNA degradation and protein oxidation levels in the brains of aging female rats, and a decrease in acetylcholinesterase activity and membrane polarization. Ultrastructural studies of the frontal cortex of exposed rats revealed that the changes were more pronounced in the aged treated rats in terms of presence of lipofuscin, vacuolization and lysosomal degradation. Our data showed that exogenous administration of E2 brought these changes to near normality in aging female rats.

Conclusions
It can therefore be concluded that E2’s beneficial effects seemed to arise from its, antioxidant and antilipidperoxidative effects, implying a therapeutic potential drug for age related changes. Based on our studies and others, we conclude that E2 have therapeutic potential for adjunctive therapy for the AD.

DOI: 10.1530/endoabs.32.P503

P504
Effects of chlorobenzenes on the histamine (HA) activated arginine-vasopressin (AVP) release – from rat pituitary cells
Zsusanna Valkus1, Zsolt Molnar2, Peter Hausinger2, Mariann Radacs2, Marta Galfi2, Regina Palfoldi3 & Bela Jojart4
1Department of Endocrinology, University of Szeged, Szeged, Hungary; 2Institute of Applied Natural Science, Faculty of Education, Department of Environmental Biology and Education, Szeged, Hungary; 3Department of Pulmonology, Szeged, Hungary; 4Department of Chemicals Informatics, Szeged, Hungary.

Introduction
The endocrine disruptor compounds (EDC), as persistent organic pollutant (POP) agents, have ability to interfere with endocrine systems. These properties of EDC may modify the homeostasis of biological organisms.

Aim
The aim was to investigate the effects of chlorobenzenes (CIB), hexachlorobenzenes + 2,4,6-trichlorobenzenes, with chronic exposure and extremely low doses on histamine mediated neuroendocrine functions.

Methods
The model-animals, Wistar male rats (bw: 80-200 g), were exposed to CIB (1.0 µg/bw kg per day) via a gastric tube for 0, 30, 60, and 90 days. After the CIB treatment, organs and bodyweight, furthermore the hepatic transferase enzymes

Endocrine Abstracts (2013) Vol 32
of Wistar rats were measured. At the completion of the in vivo treatment plasma AVP was determined by RIA, and pituitary hormones from the rat neurohypophyses were cultured. HA-stimulated AVP release was investigated in the cell cultures. The statistical analyses were performed by ANOVA.

Results
AVP secretion was increased by HA stimulation as compared to control (124.57 ± 1.39 pg AVP/mg prot) vs (43.29 ± 1.39 pg AVP/mg prot). These AVP results demonstrate that the neuro-endocrine function was significantly modulated by a chronic and subtoxic ClB treatment.

Conclusion
It can be hypothesised that ClBs may influence homeostatic processes of exposed animals through endocrine channels.

DOI: 10.1530/endoabs.32.P504

P505
Rise of obesity incidence in ChNPP accident survivors is related to abnormal secretion of α-melanotropin
Oleksii Kaminskyi, Dmytro Afanasyev, Oleksandr Kovalenko, Ludmila Derevanko, Natalia Atamanuk & Katerina Vakuluk
National Research Center for Radiation Medicine of NAMS of Ukraine, Kiev, Ukraine.

Introduction
Accident at the Chernobyl NPP (ChNPP) in Ukraine on the 26th of April, 1986 was followed by the intensive release of a wide range of radioactive elements with affinity to many endocrine tissues. The mentioned radioactive fallout resulted in both internal and external radiation exposure, among others, of the central endocrine structures of the human brain. Methods: We have conducted a retrospective analysis (20–25 years upon radiation exposure) of anthropometric indices in 606 survivors of the ChNPP accident and in 589 not exposed persons from the general population of Ukraine (i.e. control group). Basal serum levels of α-melanocyte-stimulating hormone (α-MSH), leptin and some other hormones were assayed in 100 of study subjects.

Results
Higher incidence of borderline obesity – 37% (χ² = 4.22, P = 0.04) and of primary obesity – 32.5% (χ² = 8.5, P = 0.004) was found in the ChNPP accident survivors vs persons in the control group (31.1 and 24.6% respectively). Normal body mass was more prevalent in the general population (39.3%; P = 0.002). The subgroup analysis indicated that primary obesity was more often found in ChNPP accident emergency workers of the so-called ‘non-iodine period’ of 1986–1987 (47.3%) and of ‘iodine period’ of 1986 (34.2%). For the first time there was revealed a new abnormal way of a reaction on radiation namely – the ‘blunted’ protective response of the physiological increase of α-MSH secretion along with body mass index elevation normally preventing further growth of adipose tissue. There is no increase of α-MSH secretion or even there is a hormone deficiency in most survivors of the ChNPP accident having borderline obesity or obesity.

Conclusions
Received data indicate to the increased risk of borderline obesity and obesity after the prolonged exposure to radiation in moderate doses. The mentioned risk is stipulated by disorders in melanocortin system resulting in α-MSH deficiency at the background of obesity that can be considered as a marker of such an abnormality.

DOI: 10.1530/endoabs.32.P505

P506
Endocrine functions in premenopausal and postmenopausal women
Fulden Sarac, Sumru Savas & Fehmi Akcicek
Department of Geriatrics Medicine, Ege University Medical Faculty, Izmir, Turkey.

Introduction
The anabolic hormones, namely GH, testosterone and dehydroepiandrosterone, as well as the reproductive function of women, enter a period of progressive insufficiency which is characteristically designated as somatopause, andropause and andropause respectively. The aim of the study was to compare the endocrine functions between premenopausal and postmenopausal women.

Subjects and methods
The study was included 40 premenopausal (mean age 34.9 ± 4.8 years) and 40 post menopausal women (mean age 65.1 ± 8.6 years) GH, free thyroxine (FT4), free triiodothyronine, TSH, adrenocorticotropichormone (ACTH), cortisol (COR), dehydroepiandrosteronresulfat (DHEA-S), FSH, LH, prolactin (PRL), testosterone, estradiol (E2) and fasting insulin levels were measured in all patients.

Results
Mean levels of FSH (P = 0.04), LH (P = 0.02), COR (P = 0.01), ACTH (P = 0.001) and fasting insulin (P = 0.02) in post menopausal were higher than that of premenopausal women. However, E2 (P = 0.04), TSH (P = 0.01), FT4 (P = 0.001), PRL (P = 0.05) and DHEA-S (P = 0.01) levels were lower in post menopausal than premenopausal women.

Conclusion
The study demonstrated that E2, TSH, FT4, PRL and DHEA-S levels were decreased with aging.

DOI: 10.1530/endoabs.32.P506

P507
Peutz-Jeghers syndrome with multiple endocrin failures
Runda Abdo1, Heba Sherif2, Ali Farag2, Mohamed Nadi1 & Inas Darwoish3
1Endocrinology Department, Cairo University, Cairo, Egypt; 2Hepatology Gastroenterology Department, Cairo University, Cairo, Egypt; 3Internal Medicine Department, Cairo university, Cairo, Egypt.

Introduction
Peutz-Jeghers syndrome (PJS) is a rare familial disorder with an incidence of one in 12–30,000 live births characterized by mucocutaneous pigmentation, gastrointestinal and extra gastrointestinal hamartomatous polypos and an increased risk of malignancy. Case presentation
We report a 22-year-old female hypothyroid since age of 4, type 1 diabetic since age of 11, who presented with melena. Pigmentation of the buccal mucosa, multiple lipomatosis, vitamin D deficiency. Upper endoscopy, colonoscopy, enteroscope revealed multiple polyps. In stomach pyloric ring, rectum biopsy showing hamartomatous polyp.

Conclusion
A case of peutz Jeghers syndrome with multiple lipomatosis, she is type 1 diabetic with early childhood hypothryoidism, vitamin D deficiency. These combinations of different aetologies in the same patient might raise the suspension of a new syndrome waiting for other observational studies.

Keywords: peutz-Jeghers syndrome; type 1 diabetes; hypothryoidism; multiple lipomatosis

DOI: 10.1530/endoabs.32.P507

Endocrine tumours and neoplasia
P508
Hereditary forms of medullary carcinoma of the thyroid: about a new family
Nora Soumeya Fedala1, Farida Chentli1, Fatima Saraoui1, Lakhdar Griene2 & Mohamed Chakouche2
1Endocrinology Bab El Oued Hospital, Algiers, Algeria; 2Hormonology Cpmc Hospital, Algiers, Algeria.

The medullary carcinoma of thyroid is rare and represent 5–10% of the thyroid cancers. It appears under sporadic and family forms in more than a third of cases. It becomes integrated them into the multiple endocrine neoplasms type 2 of autosomique dominant transmission associate with germinal mutations of the gene RET. We bring report in this study, the observation of a new family shape, BL index case was diagnosed in the age of 42 years further to the appearance of a severe HTA associated with renal colics and a goiter. The paraclinic assessment reveals a bilateral phochromocytoma, a medullary carcinoma and a primary hyperparathyroidism. The molecular study of RET gene reveals a germlmal mutation of C634R (TGTCGC) exon 11. Bilateral surrenallectomy is realized followed by a thyroidectomy and parathyroidectomy. The evolution is marked by sudden death of the patient with recurrence of phochromocytoma. A family investigation was indicated. Unfortunately, only eight subjects agreed to submit themselves to the exploration. All were affected and presented the same paintings phenotype and genotype. Prevalence of the medullary
carcinoma family of novo is estimated between 5 and 16% of cases. So molecular analyses of gene RET must be realized systematically. This allows a early diagnosis and a specific and preventive care. 0.634 mutations is the most frequent and finds itself in more than two thirds of the cases with a correlation phenotype genotype. The risk of phaeochromocytoma, hyperparathyroidism and aggressiveness of tumors are higher when patients are affected by this mutations.

DO: 10.1530/endoabs.32.P508

P509

Abstract unavailable.

DO: 10.1530/endoabs.32.P509

P510

Adrenocortical carcinoma: a population-based study on incidence and survival in the Netherlands since 1993

Thomas Kerkhofs1, Rob Verhoeven2, Jan-Maarten van der Zwan3, Jeanne Dieleman1, Michiel Kersi4, Thera Links4, Lonneke van de Poll-Franse2 & Harm Haak1

1Maxima Medical Centre, Eindhoven/Veldhoven, The Netherlands; 2Comprehensive Cancer Centre South, Eindhoven, The Netherlands; 3Maxima Medical Centre the Netherlands, Utrecht, The Netherlands; 4University Medical Centre Groningen, Groningen, The Netherlands.

Introduction

Adrenocortical carcinoma (ACC) has a reported annual incidence of 0.5–2.0 cases per million individuals. Updated population-based studies on incidence are lacking. The aim of this nationwide survey was to describe the incidence and survival rate of ACC in the Netherlands. Secondary objectives were to evaluate changes in survival rates and in the number of patients undergoing surgery.

Methods

All ACC patients registered in the Netherlands Cancer Registry between 1993 and 2010 were included. Data on demographics, stage of disease, primary treatment modality and survival were used.

Results

Included were 359 patients, of whom 196 were female (55%). Median age at diagnosis was 56 (range 1-91) years. The 5-year age-standardized incidence rate decreased from 1.3 to 1.0 per one million person-years. Median survival for patients with stage I-II, stage III and stage IV was 159 months (95% CI 93–225 months), 26 months (95% CI 4–49 months) and 5 months (95% CI 2–8 months) respectively (P < 0.001). Improvement in survival was not observed, as reflected by the lack of association between survival and time of diagnosis. The percentage of patients receiving treatment increased significantly from 76% in 1993–1998 to 83% in 2005–2010 (P = 0.047), mainly explained by an increase in surgery in stage III–IV patients.

Conclusion

These nationwide data provide an up to date description of ACC epidemiology in the Netherlands. A trend towards a decreasing overall incidence rate was observed. Survival rates did not change during this period despite an increased number of surgical procedures.

DO: 10.1530/endoabs.32.P510

P511

Investigation of novel chemotherapeutic combinations in a tumor model for adrenocortical carcinoma

Sara Jung1, Constanze Hanelt1, Thomas Mussack1,2, Martin Reineck1 & Felix Beuschlein1

1Endocrine Research Unit, Medizinische Klinik and Poliklinik IV, Ludwig-Maximilians-University, Munich, Germany; 2Department of Surgery, Ludwig-Maximilians-University, Munich, Germany.

Medical treatment of adrenocortical carcinoma (ACC) is limited to common cytotoxic agents, which are usually given in combination with mitotane (M). Recently, we investigated together with M the effects of i) the classical EDP protocol (etoposide, doxorubicin, and cisplatin) and ii) a novel paclitaxel containing scheme PDP (paclitaxel, doxorubicin, and cisplatin) on human NCIh295 cells indicating anti-tumoral superiority of PDP-M over EDP-M regarding cell viability (P = 0.001), apoptosis (P = 0.001) and proliferation (P < 0.01). Since we found further evidence for an extraordinary uptake phenomenon of liposomes by ACC cells we included for consecutive in vivo experiments liposomal variants called LEDP-M (etoposide, liposomal doxorubicin, and liposomal cisplatin) and LPDP-M (nab-paclitaxel, liposomal doxorubicin, and liposomal cisplatin). In short-term therapeutic experiments on NCIh295-xenographs EDP-M did not induce a significant loss of tumor cells while PDP-P (P < 0.01) and LPDP-M (P < 0.01) resulted overall in significant tumor cell reduction compared with controls. LEDP-M (P < 0.01) and LPDP-M (P < 0.05) induced furthermore apoptosis as quantified by TUNEL staining. Similar effects were detectable with TUNEL on patient’s ACC-xenographs comparing LPDP-M with PDP-M (P < 0.01), but not between EDP-M and LEDP-M. Blood counts of PDP-M and LPDP-M treated mice showed a tendency to leucocyte reduction without statistical significance vs controls, while EDP-M and LEDP-M treatments lead to leucopenia (P < 0.01). HE-stained kidneys from LEDP-M and LPDP-M treated mice appeared unaffected compared with controls, while kidneys of EDP-M and PDP-M groups showed by trend reduced nuclear staining intensities and more diffuse cell borders. Long-term experiments on NCIh295-xenographs revealed highest and sustained anti-tumoral effects for LEDP-M. Beside significant differences in tumor sizes between controls and LEDP-M, we detected beginning from day 35 (P < 0.05) up to day 53 (end of experiment, P < 0.001) highly significant reduced tumor sizes for LEDP-M compared with EDP-M. In summary, liposomal chemotherapies could represent promising approaches that would deserve testing in clinical protocols for patients with ACC.

DO: 10.1530/endoabs.32.P511

P512

Biochemical diagnosis of phaeochromocytoma using plasma free normetanephrine, metanephrine and methoxytyramine: importance of supine sampling under fasting conditions

Roland Dürre1, Mirko Petzsch1, Christina Pamporaki1, Aleksander Prebihs2, Martin Fassnacht3, Felix Beuschlein4, Hartmut Neumann4, Andrzej Januszewicz5, Jacques Lenders6,1 & Graeme Eisenhofer1

1University Hospital Dresden, Dresden, Germany; 2Institute of Cardiology, Warsaw, Poland; 3University Hospital Würzburg, Würzburg, Germany; 4Medical Clinic Innenstadt, LMU, Munich, Germany; 5University of Freiburg, Freiberg, Germany; 6Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands.

Objective

To document influences of sampling of blood under supine fasting versus seated non-fasting conditions on diagnosis of pheochromocytomas using plasma concentrations of normetanephrine, metanephrine and methoxytyramine (P-NMN/MN/MTY).

Design and methods

P-NMN/MN/MTY were measured by liquid chromatography with tandem mass spectrometry in 695 patients at five centers, two of which complied with requirements for supine sampling after an overnight fast and three of which did not. Pheochromocytomas were found in 109 patients (60 non-compliant, 49 compliant). Use of upper-cut-offs calculated for compliant conditions was substantially higher under non-compliant compared to compliant conditions for P-NMN/MN/MTY (17.3 vs 12.4 pg/ml) in patients without tumors. Upper cutoffs were also higher under non-compliant compared to compliant conditions for P-NMN/MN/MTY did not differ under supine sampling under fasting conditions and not in 586 patients (144 non-compliant, 442 compliant).

Results

To document influences of sampling of blood under supine fasting versus

Conclusions

P-NMN/MN/MTY in patients with pheochromocytomas did not differ under compliant and non-compliant conditions. However, sampling under non-compliant conditions resulted in 50 and 40% higher (P < 0.001) median plasma concentrations of MN (84 vs 56 pmol/ml) and MTY (17.3 vs 12.4 pg/ml) in patients without tumors. Upper cut-offs were also substantially higher under non-compliant compared to compliant conditions for both MN (241 vs 144 pmol/ml) and MTY (62 vs 33 pg/ml). Differences for MN were minimal. Use of upper-cut-offs calculated for non-compliant compared to compliant conditions resulted in substantially decreased diagnostic sensitivity (88.1 vs 98.2%). Use of upper-cut-offs calculated for compliant conditions was
The embryonic transcription factor \( TBX1 \) is expressed in adult parathyroid cells and might be involved in parathyroid tumorigenesis.

Cancer cells and embryonic stem cells share many key biological properties and have common genetic signature: transcription factors regulating self-renewal and differentiation have been found expressed in human cancer cells. We focused our attention on \( TBX1 \), the gene involved in 22q11.2 microdeletion/DiGeorge syndrome, which is involved in heart, thymic and parathyroid cells differentiation.

Real-time PCR, western blot and immunohistochemistry demonstrated that \( TBX1 \) mRNA and protein were expressed in normal parathyroid glands (\( n = 3 \)). Immunofluorescence (IF) showed a positive staining in parathyroid PTH + cells with a cytoplasmic and nuclear localization. Typical parathyroid adenomas (\( n = 25 \)) expressed \( TBX1 \) at higher levels than normal glands. The regulation and the role of \( TBX1 \) gene in parathyroid adenomas were further investigated. Functional studies were performed in HEK293 cells, since they expressed \( TBX1 \) mRNA and protein. We tested the hypothesis that \( TBX1 \) expression might be regulated by signaling pathway involved in embryogenesis such as BMP/SMAD and Wnt/\( \beta \)-catenin. Treatment for 3–16 hours with 20 ng/ml BMP4 increased \( TBX1 \) mRNA levels. Interestingly, we found by IF that tumoral parathyroid cells expressed the BMP4 receptor BMPR1A. By contrast, \( TBX1 \) mRNA levels were inhibited by \( \beta \)-catenin accumulation induced by 8-hours of treatment with 10–20 nM lithium chloride. Furthermore, the activation of the calcium sensing receptor (CaSR) by stimulatory 24 hours HEK293 cells stably transfected with the human CaSR, with increasing calcium as well as R568 concentrations, the CaSR agonist cinacalcet, induced a reduction in \( TBX1 \) mRNA levels. Silencing of \( TBX1 \) gene in both HEK293 and tumoral parathyroid cells induced a significant reduction in \( TBX1 \) target genes such as WNT5a and BMP4-induced increase in inhibitor of differentiation-1 (Id1) mRNA expression levels. Conclusion, an embryonic signature has been identified in adult parathyroid cells and it is suggested to be involved in parathyroid tumorigenesis. New potential therapeutic targets for parathyroid tumours have been discovered.

DOI: 10.1530/endoabs.32.P513

P514

Characterization and sub-cellular localization of somatostatin receptors in DU-145 and PC-3 human androgen-independent prostate cancer cells: effect of mono- and bi-specific somatostatin analogs on cell growth

Somatostatin (SRIF) is an inhibitory hormone that plays a regulatory role in several cell functions including cell proliferation. SRIF acts through five specific membrane receptors (sst1-5), expressed on SRIF-target cells. SRIF and sst may play a significant role in the progression and neuroendocrine differentiation of human prostate cancer (PCa). However, conflicting results have been reported in the literature on ssts heterogeneity and specific cell localization in PCa. Aim of this study was to evaluate in two androgen-independent human PCa cell lines DU-145 and PC-3: cells: (a) the gene and protein expression of ssts; (b) the sub-cellular localization of the different ssts; (c) the effects of new mono- and bispecific SRIF analogs (SSAs) on cell proliferation and activation of proteins involved in the regulation of the cell cycle; (d) the constitutive and SSAs sst dimerization. DU-145 and PC-3 cells express all SRIF receptors at both gene (SSTR1-5) and protein (sst1-5) levels. Moreover, sst1/sst2 and sst2/sst5 receptor dimers were constitutively present at the cell membrane. A 48 h treatment with BIM-23704 (sst1/sst2) and BIM-23244 (sst2/sst5) compounds increased the amount of sst1/sst2 and sst2/sst5 dimers, respectively. Sub-cellular organelle separation of cell lysates showed a different sst1, sst2 and sst5 nuclear, lysosomal and microsomal distribution, according to the different recycling dynamics of these isoforms. In DU-145 and PC-3 cells, a 48 h treatment with BIM-23244 (sst2/sst5) and BIM-23926 (sst1) analogs were more effective in inhibiting cell proliferation (\( \geq 96\% \)) in the dose-range tested (10 \( \mu \)M–10 \( \mu \)M), compared to BIM-23120 (sst2), BIM-23206 (sst5) and BIM-23704 (sst1/sst2) compounds. Moreover, in DU-145 cells BIM-23244 and BIM-23926 activated p21 and phosphorylated ERK, two proteins involved in cell cycle arrest. In conclusion, DU-145 and PC-3 cells represent a useful PCA model for studying sst trafficking/regulated, intracellular subtype-linked signaling, and validating new sst-specific SRIF analogs aimed at PCa treatment.

DOI: 10.1530/endoabs.32.P514

P515

Prevalence of P30L, V281L and P453S mutations of CYP21 gene in patients with nonfunctional adrenal incidentalomas

Clinically apparent adrenal masses (incidentalomas) are detected incidentally by imaging procedures in 0.5–4.5% of the general population. Diagnostic process identifies functional and potentially malignant tumors. Adrenocortical tumors are those malignancies that are the most common hormone-producing tumors, the differentiation of which is based on functional tests, which in 75%–90% of cases, are positive. However, among nonfunctional adenomas, the percentage of tumors that are actually malignant is not well known. Several studies have shown that 50% of patients with adrenal incidentalomas (AI) carry mutations of the CYP21 gene, in which 10% of patients have isolated mutations of the CYP21 gene. The most common mutations of CYP21 are P30L, V281L and P453S. The aim of this study was to evaluate the relationship between these mutations carriers and prevalence of adrenal incidentalomas and their clinical picture.

Introduction

The total number of 100 adult patients at the age of 20–70 years with adrenal incidentalomas discovered in Computed Tomography or Magnetic Resonance Imaging were enrolled into the study after exclusion of hormonal function of the tumor. Many clinical, biochemical and imaging data were analyzed. Direct sequencing of CYP21 gene was performed to detect P30L, V281L and P453S mutations in all subjects and in the control group of 100 neonates. ACTH (Synacthen) stimulation test was carried out in all mutation carriers and among 30 randomly chosen noncarriers with adrenal incidentalomas.
Results
Eight subjects were identified to be heterozygous carriers of CYP21 gene mutations (three of P310L, three of P453S and two of V281L), whereas no mutations were detected in the neonates’ control group (OR = 8.7; P = 0.0039).

Conclusion
For the first time, we report on the clinical relevance of CYP21 gene mutations in the offspring of p27-mutated mothers. In conclusion, we propose to perform mutation analysis on the p27 gene in adolescent girls with signs of precocious puberty. The study clearly shows the need for further research in this field.

DOI: 10.1530/endoabs.32.P516

**P517**

The bone morphogenetic protein 7 (Bmp7) plays a pro-tumorigenic role in pheochromocytoma

Ines Repokis1,2, Ines Höög3, Natalia Anastasov3, Felix Beuschlein4, Michael J Atkinson1,5 & Natalia Pellegrini

1Pathology, Helmholtz Zentrum München, Neuherberg, Germany; 2Radiation Biology, Helmholtz Zentrum München, Neuherberg, Germany; 3Radiation Oncology, Technical University Munich, Munich, Munich, Germany; 4Endocrine Research Unit, Munich, Munich, Germany.

Introduction
Rats carrying a germline loss-of-function mutation in p27 (MENX syndrome) develop bilateral pheochromocytoma (PCC) with complete penetrance. Gene expression profiling of rat PCCs identified genes highly expressed in tumors vs normal adrenal medulla. Several of them were found up-regulated also in human PCCs (both sporadic and familial), including the BMP7 gene encoding a member of the bone morphogenetic protein family. BMP7 has been shown to be involved in other human cancers, but its role in PCC tumorigenesis is unknown.

Methods
We used cell lines such as PC12 (rat PCC), with low endogenous levels of Bmp7, and MPC (mouse PCC) and its aggressive derivative MTT, both with high levels of Bmp7. We also use primary rat PCC cells with high levels of Bmp7, Bmp7-expressing plasmid was transfected in PC12 cells. Bmp7 gene knockdown in MPC/MTT cells and primary rat cultures was performed using lentiviral vector expressing anti-Bmp7 shRNA molecules. In vitro assays assessing proliferation (MTT), migration and invasion (Boyden chamber) were then performed. We analyzed the link between p27 and Bmp7 in embryonic fibroblast cells with either mutant or knocked-out p27 or in sip27- transfected PC12 cells.

Results
We observed that up-regulation of Bmp7 enhances proliferation, migration and invasion of the PC12 cells, while down-regulation of Bmp7 impairs these properties in MPC and MTT cells.

Conclusion
In conclusion, we observed that Bmp7 promotes the tumorigenic phenotype of PCC cells and that its level is influenced by the amount of p27. BMP7 represents a novel target for therapy of PCC since the knock-down in vitro shows promising impairment of the tumorigenic phenotype.

DOI: 10.1530/endoabs.32.P517

**P518**

Neuroendocrine tumours (NETs) of lung: new data on atypical carcinoid and large cell neuroendocrine carcinoma from a French-Italian multicentric study

Francesca Marcilli1, Olaf Mercier2, Piero Feralia3, Planchard David4, Pier Luigi Filosso5, Alain Chapelier6, Franco Grimoldi7, Bertrand Richard de Latour8, Giussy Bianco9, Joel Guigay10, Gulcaglino Monaco11, Philippe Darieville12, Mauro Papotti13, Jean-Yves Scavazec14, Annamaria Colao1, Eric Baudin15 & Antonigioi Fagigiano12.

1University of Naples Federico II, Naples, Italy; 2Marie Lannelongue Hospital, Le Plessis Robinson, France; 3University of Perugia, Perugia, Italy; 4Institute Gustave Roussy, Villejuif, France; 5University of Turin, Turin, Italy; 6Foch Hospital, Suresnes Hauts-de-Seine, France; 7Santa Maria della Misericordia, University of Udine, Udine, Italy; 8Pontchaillou Hospital, University of Rennes, Rennes, France; 9Mediterranean Institut of Oncology, Viagrande, Italy; 10University of Turin at St Luigi Hospital, Orbassano, Turin, Italy; 11Cardarelli Hospital, Naples, Italy; 12National Cancer Institute G.Pascale Foundation, Naples, Italy.

Introduction
Natural history of lung neuroendocrine tumours (NETs) and in particular of two histological subtypes, atypical carcinoid (AC) and large cell neuroendocrine carcinoma (LCNEC), is poorly known.

Aim of the study was to determine disease-free survival (DFS) and overall survival (OS) of sporadic, resectable, non-metastatic lung AC and LCNEC.

Endocrine Abstracts (2013) Vol 32
Patients and methods
This retrospective study involved 116 consecutive patients surgically treated (R0) between 1998 and 2008 for AC and LCNEC in two Italian and French expert networks. Slides were reviewed by two expert pathologists to validate the pathological definition (WHO 2004).

Results
The files of 86 patients were reviewed (49 males and 37 females). Mean age at diagnosis was 58 ± 15 years for AC and 63 ± 15 years for LCNEC. The most frequent presenting symptom was respiratory infection (AC: 24%, LCNEC: 31%); endocrine syndrome occurred in only one AC patient (Cushing’s syndrome). Mean follow-up time was 80.6 months in AC and 50.6 months in LCNEC. The most used surgery was lobectomy (AC: 81%, LCNEC: 59%). N-positive status was found in 29 and 57% of AC and LCNEC respectively. The rate of recurrence was 39% among AC (15% local, 24% distant metastasis) and 41% in LCNEC (27% local, 14% distant metastasis). The mean time of recurrence from surgery was 24.6 months in AC and 15 months in LCNEC. Median OS was 9.4 years in AC (not reached in AC). Median DFS was not reached in both histotypes. Recurrence rate was higher in N+ AC patients than in N0 ones (76 vs 24%).

Conclusion
Patients with lung AC and LCNEC experience a high rate of recurrence after surgery. Beside LCNEC patients, N-positive AC patients should be considered for adjuvant therapy and be subjected to an intensive monitoring on. A better definition of lung NETs prognosis and natural history is expected from large collaborative studies.

DOI: 10.1530/endoabs.32.P518

P519
mTOR, AKT, p70S6K and ERK1/2 levels predict sensitivity to mTOR and PI3K/mTOR inhibitors in human bronchial carcinoid
Teresa Gagliano1, Mariaeruccia Bellio1, Erica Gentili1,2, Daniela Molè1,2, Federico Tagliafieri1, Marco Schiavi1, Narciso Giorgio Cavalleocco1, Fiorella Calabrese1, Maria Rosaria Ambrosio1, Federico Rea2, Ettore degli Uberti1,3, Maria Chiara Zatelli1,3
1Section of Endocrinology, University of Ferrara, Ferrara, Italy; 2University of Padua, Padua, Italy; 3Laboratorio in rete del Tecnoopolo “Tecnologie delle terapie avanzate” (LTTA) of the University of Ferrara, Ferrara, Italy.

Background
Bronchial carcinoids (BICs) are rare neuroendocrine tumors that are still orphan of medical treatment. Human BC primary cultures may display resistance to everolimus, an inhibitor of the mammalian target of rapamycin (mTOR), in terms of cell viability reduction.

Aim
To assess whether the novel dual PI3K/mTOR inhibitor, NVP-BEZ235, may be effective in everolimus-resistant human BC tissues and cell lines. In addition, we search for possible markers of mTOR inhibitors efficacy, that may help in identifying the patients that may benefit from mTOR inhibitors treatment, sparing them from ineffective therapy.

Results
NVP-BEZ235 is twice as potent as everolimus in reducing cell viability and activating apoptosis in human BC tissues that display sensitivity to mTOR inhibitors, but is not effective in everolimus-resistant BC tissues and cell lines, that by-pass cyclin D1 down-regulation and escape G0/G1 blockade. Rebound AKT activation was not observed in response to treatment with either mTOR inhibitor in resistant BC cells. We also show that, in addition to total mTOR levels, putative markers of BC sensitivity to mTOR inhibitors are represented by higher AKT, p70S6K and ERK1/2 protein levels.

Conclusion
These data indicate that the dual PI3K/mTOR inhibitor NVP-BEZ235 is more potent than everolimus in reducing human BC cell proliferation. ‘Resistant’ cells display lower levels of mTOR, AKT, p70S6K and ERK1/2, indicating that these proteins may be used as predictive markers of resistance to mTOR and PI3K/mTOR inhibitors in human BC.

DOI: 10.1530/endoabs.32.P519

P520
Assessment of fatal events in patients with radio-active iodine (RAI)-refractory differentiated thyroid cancer responsive to treatment with sorafenib
Vincenzo Marotta1, Michela Del Prete1, Valeria Ramundo1, Francesca Marcì llo1, Antonella Di Sarno2, Raffaella Eposito1, Annachiara Carratu1, Chiara de Luca di Roseto1, Luigi Camera1, Annamaria Colao1 & Antongiulio Faggiano2
1Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy; 2I. Infectious Disease and Interventional Ultrasound Unit, “D. Cotugno” Hospital, Naples, Italy; 3Department of Biomorphological and Functional Sciences, Federico II University, Naples, Italy; 4Endocrinology, National Cancer Institute, “Fondazione G. Pascale”, Naples, Italy.

Introduction
Targeted therapy with the multi-kinase inhibitor sorafenib is effective for treatment of differentiated thyroid cancer (DTC) unresponsive to RAI. Although kinase-inhibitors (KIs) are usually well tolerated, severe and even fatal adverse events are reported. Aim of the study was to assess incidence and characteristics of fatal events in patients with RAI-refractory DTC responsive to treatment with sorafenib.

Design
A retrospective analysis of patients with progressive iodine-refractory DTC subjected to off-label treatment with sorafenib in our centre was performed. Radiological response was assessed according to RECIST criteria version 1.1.

Results
From March 2010, 17 patients affected with RAI-refractory DTC were subjected to treatment with sorafenib. Of them, 12 subjects were responsive to treatment (seven achieved stable disease and five partial response). Median of treatment for responding patients was 14 months. Fatal events were reported in five of 12 patients (42%). Three patients died from severe haemorrhage of the upper respiratory tract after 4 months of treatment. They had a wide tracheoesophageal neoplastic infiltration previously treated with external beam irradiation. Two subjects died from cardiac arrest after 10 months of treatment. They had developed a moderate hypertension after starting treatment with sorafenib.

Conclusions
Although treatment with sorafenib is effective in most patients affected with RAI-refractory DTC, it could be responsible of fatal events. Particularly, bleeding events and cardiac damage are considered as specific adverse events in subjects treated with KIs. In light of this, we suggest to exclude from treatment, or to use a reduced dosage, in those patients with mucosal neoplastic infiltration and those previously treated with radiotherapy. Furthermore, a careful and individualized cardiovascular management is mandatory.

DOI: 10.1530/endoabs.32.P520

P521
Diagnosis of endogenous hyperinsulinism through arterial calcium stimulation with hepatic venous sampling
Paloma Moreno Moreno1, María Rosa Alhambra Exposito1, Luis Zurera Tendero1,2, Rafael Palomares Ortega1, María Angeles Gálvez Moreno1 & Pedro Benito López2
1Servicio de Endocrinología y Nutrición, Reina Sofia University Hospital, Córdoba, Spain; 2UGC de Radiodiagnóstico. Reina Sofia University Hospital, Córdoba, Spain.

Objective
The aim of this study was to assess the utility of arterial calcium stimulation with hepatic venous sampling (ASVS) in the localization of tumors in patients with endogenous hyperinsulinism not detected with other methods.

Patients and methods
We performed a retrospective study of 30 patients admitted to our hospital for hypoglycemia who underwent ASVS because the source of hyperinsulinism was not clearly identified by other imaging techniques. The histopathological results in patients who underwent a surgical procedure were considered the reference for statistical study of the accuracy of this technique. Statistical analysis was performed by comparing proportions with the χ2 test with Yates’ correction for contingency tables, and Cohen’s k coefficient as a measure of interrater agreement between two observations.

Results
Surgery was performed in 21 patients, 20 with positive ASVS and the remaining

Endocrine Abstracts (2013) Vol 32
one with negative result. Endogenous hyperinsulinism (insulinoma and nesidioblastosis) was removed in 19 patients, and all of these were detected in the ASVS. A total of 95% of the positive ASVS test were diagnosed of endogenous hyperinsulinism (80% insulinoma and 15% nesidioblastosis), and 100% of endogenous hyperinsulinism had a positive result of the ASVS being this association statistically significant ($\chi^2 = 15.771; P < 0.001$). A good and statistically significant agreement was obtained between histopathologic diagnostic and ASVS results ($K = 0.518, P < 0.001$).

Conclusions
ASVS is a useful procedure in the localization diagnosis of endogenous hyperinsulinism not detected by other imaging tests. This technique allows tumors in the pancreatic gland to be identified and may be useful in the choice of the surgical technique to be used.

DOI: 10.1530/endoabs.32.P521

P522
Localization of pathological parathyroids in patients with thyroid abnormalities by PTH measurements in fine needle aspiration biopsy washouts
Bozena Popowicz, Stanisław Sorny, Joanna Jankiewicz-Wika, Mariusz Klenció & Dorota Slowinska-Klencio
Medical University of Lodz, Lodz, Poland.

Preoperative localization of the pathological parathyroid gland is critical in the clinical evaluation of patients with primary hyperparathyroidism (PHP) before surgical resection. Unfortunately, scintigraphy nor ultrasound-guided FNAB do not show enough accuracy in this respect, especially in patients with concurrent thyroid pathology. The aim of the investigation was to assess the usefulness of measurements of PTH concentration in FNAB washouts (PTH-FNAB) in diagnosing PHP in patients with thyroid nodules or chronic thyroiditis. The study included 50 patients with a focal lesion that was suggestive in ultrasonography for parathyroid gland, 40 patients with clinical and/or biochemical picture of PHP and ten patients with a suspicion for parathyroid incidentaloma. Simultaneously biopsied thyroid nodules were the internal controls.

Mean serum PTH concentration was $310.9 \pm 393.9$ pg/ml (mean $\pm$ SD). Positive PTH-FNAB (PTH-FNAB concentration – after dilution of a specimen in 1 ml 0.9% NaCl – higher than in serum) was observed in 40 patients (80.0%). Mean positive PTH-FNAB $\pm$ SD was $2822.41 \pm 2061.29$ pg/ml. Mean negative PTH-FNAB was significantly lower ($12.3 \pm 8.7$ pg/ml, $P < 0.0002$) and similar to that in the internal controls. Negative predictive value (NPV) of classical FNAB vs PTH-FNAB was 26.5%, NPV of scintigraphy vs PTH-FNAB was 46.2%, NPV of PTH-FNAB vs scintigraphy was 66.7%. No false negative result of PTH-FNAB vs classical FNAB was noted. Lower frequency of positive PTH-FNAB was observed when the thickness of the thyroid lobes was $> 20$ mm (50.0 vs 87.5%, $P < 0.05$) and when the thickness of a lesion suspected for parathyroid pathology was $\leq 5$ mm (66.7 vs 93.3%, $P < 0.05$). The negative influence of chronic thyroiditis was less marked (73.9 vs 85.2%). Surgical removal of the parathyroid lesion was performed in 20 patients (five cases of hyperplasia, 14 adenomas, and one parathyroid cancer). No false positive PTH-FNAB was observed in that group and only one false negative result was noted in a patient with large nodular goitre.

Measurement of PTH concentration in the FNAB washouts allows to identify pathological parathyroids in patients with thyroid abnormalities more effectively than scintigraphy and classical ultrasound-guided FNAB.

DOI: 10.1530/endoabs.32.P522

P523
Six-years experience in the treatment of the neuroendocrine tumors with the use of peptide receptor radionuclide therapy (PRRT)
Anna Sowa-Staszczak, Agnieszka Stefanska, Monika Tomaszuk, Aleksandra Gilis-Januszewska, Dorota Pach, Renata Mikolajczak & Alicja Hubalewska-Dydejczyk
1Department of Endocrinology, Jagiellonian University Medical College, Krakow, Poland; 2Radioisotope Center POLATOM, National Centre for Nuclear Research, Otwock, Poland.

Introduction
The aim of this study was to assess the efficacy of peptide receptor radionuclide therapy (PRRT) with the use of $^{90}$Y-DOTATATE and the survival rate of patients with disseminated or non-operable neuroendocrine tumors (NETs).

Methods
In the time period from June 2006 to October 2012, 70 patients were treated with PRRT in our department. The $^{90}$Y-DOTATATE therapeutic activity was calculated per total body surface area up to a total of 7.4 GBq/m$^2$ administrated in three to five cycles, repeated every 4–9 weeks. Before and after the therapy, blood tests for hematology, kidney and liver function were performed. After PRRT, patients have been further treated with cold long acting somatostatin analogues (Sandostatin LAR) to the progression of the disease.

Results
Out of 70 $^{90}$Y-DOTATATE treated patients, 22 died after completing the therapy, among them two due to myocardial infarction. After 12-month follow-up, stabilization of the disease was observed in 63%, partial remission in 25%, and progression in 12% in this group of patients. The progression-free survival (PFS) was found to be 41.27 months and the event-free survival (EFS) 37.73 months. The median overall survival (OS) was not reached. During follow-up, transient decrease in PLT, WBC and hemoglobin values was observed. A increase in creatinine level and decrease in GFR values over observation period were found, but these were clinically insignificant symptoms of transient nephrotoxicity.

Summary
Long-term patients benefit in the form of long survival rate, symptomatic relief and tumor mass reduction after $^{90}$Y-DOTATATE therapy was observed. PRRT is safety method and may extend the survival of disseminated patients with NETs.

DOI: 10.1530/endoabs.32.P523
The expression of SSTR dominant negative truncated variant sst5MD4 influences the effects of SOM-230 on prostate cells in vitro

Valentina Rossi1, Daniela Visconti2, Cristina De Rosa2, Ciro Abbondanza2, Iolanda Cioffi3, Assunta De Masì4 & Antonio Agostino Sinisi2

1Ypsilon Biotechnology snc, Napoli, Italy; 2Dpt Patologia Generale, Second University of Napoli, Napoli, Italy; 3Dpt Scienze Cardiotoraciche e Polmonari, U. Endocrinologia, Second University of Napoli, Napoli, Italy.

Introduction

The presence of truncated variant of somatostatin receptors (SSTR) has been demonstrated in pituitary tumours. These variants seem act as dominant negative of SSTR and induce the resistance to SST analogue (SSTA) treatment. A variant of SSTR5, sst5MD4, has been found to disrupt SST signalling in breast cancer cells. In present study, we assayed the expression of sst5MD4 in two non-transformed epithelial prostate cell lines (EPC): EPN, derived from a normal surrounding area of a prostate tumour, and CPEC, derived from the core of a prostate cancer tissue. In these cells, we evaluated the effects of SOM-230 (Novartis, Basilea, SW), a SSTA pan ligand with strong affinity for SSTR2 and 5.

Cell cultures starved in red phenol-free DMEM and 1% charcoal treated FBS for 5 d were treated either with 10-6 SOM-230 or 10-8 SOM-230. After 24/48 h, cells were harvested for RT-PCR and for SDS-PAGE/western blot, or labelled with [3H]thymidine for cell cycle analysis by flow cytometer.

Results

SSTR2 and 5 were equally expressed in both cell lines. SSTR1 and 3, and sst5MD4 mRNA levels were higher in CPEC than in EPN (P < 0.001). In EPN, SOM-230 induced a significant caspase-dependent apoptosis, a reduction of S-phase proliferation together with an increase in bc21 and a decrease in c-myc expression. In CPEC cells, SOM-230 treatment resulted in a modest apoptosis induction and a slight inhibition of cell growth, without changes of bc21 and c-myc levels.

Conclusions

sst5MD4 variant is differently expressed in the EPC lines studied here. SOM-230 is effective in the control of cell growth in EPN cultures, while the reduced apoptotic response and the lack of growth arrest observed in CPEC could be due to presence of high levels of sst5MD4 interfering with SST signalling.

DOI: 10.1530/endoabs.32.P524

P525

Function and origin of tumour-associated fibroblasts (TAFs) in human parathyroid neoplasia

Chiara Verdelli1, Laura Avaglano2, Vito Guarneri3, Alfredo Scillitani4, Elena Passini2, Leonardo Vicentini5, Giovanna Battista Stefano1, Anna Spada1, Gaetano Bulfamante1 & Sabrina Corbetta6

1Molecular Biology Laboratory, IRCCS Policlinico san Donato, San Donato Milanese (MI), Italy; 2Department of Obstetrics and Gynecology, DMSD San Paolo, University of Milan, Milan, Italy; 3Medical Genetics, IRCCS Hospital Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), Italy; 4Endocrine Unit, IRCCS Hospital Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), Italy; 5Endocrine Unit, Department of Biomedical Sciences for Health, University of Milan, IRCCS Policlinico San Donato, San Donato Milanese (MI), Italy; 6Endocrine Surgery, Fondazione IRCCS Ca’ Granda-Ospedale Maggiore Policlinico-Milano, Milan, Italy; 7Surgery 1, University of Milan, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milan, Italy; 8Human Pathology, DMSD San Paolo, San Paolo Hospital Medical School, University of Milan, Milan, Italy.

Tumour-associated fibroblasts (TAFs) are important players in tumour formation, growth, enhancement and metastasis. We firstly investigated the TAFs component in human parathyroid neoplasia from patients with primary hyperparathyroidism. Alpha-smooth muscle actin (alpha-SMA) has been used to identify activated TAFs (myofibroblasts). Culturing explants from parathyroid adenomas (PA, n = 5), large spindle-shaped alpha-SMA+ cells outgrew from explants and the expression of activated fibroblasts markers such as vimentin, stromal derived factor-1 (SDF-1/CXCL12) and fibroblast activated protein were detected. Immunohistochemistry showed alpha-SMA+ cells highly represented in normal parathyroid glands (n = 3) where they lined the acinar structures. In typical PAs (n = 5) alpha-SMA+ cells were variably reduced, though they surrounded new microvessels suggesting a role in neangiogenesis. Interestingly, in human fetal parathyroids (19–24 weeks of gestation), myofibroblasts were exclusively found lining blood vessels. In atypical adenomas (n = 3) and carcinomas (n = 3), the chief cells proliferating in sheets were not sustained by myofibroblasts, which were highly represented in the fibrous bands and capsula stroma, suggesting a role of alpha-SMA+ cells in invasiveness.

Coculture of human bone-marrow mesenchymal stem cells (hBM-MSCs) with PA-derived explants (n = 3) induced significant increases of VEGFa mRNA expression levels in hBM-MSCs. Immunofluorescence (IF) and FACS (n = 5) identified 32–63% of PA-derived cells expressing CXCR4, the SDF-1 receptor, whose 47–90% coexpressing PTH and CXCR4. Treatment of cocultures with the CXCR4 antagonist AMD3100 reduced the coculture-stimulated VEGFa mRNA expression in hBM-MSCs, suggesting that the proangiogenic effect might be regulated through the CXCR4/SDF-1 pathway. A subset of alpha-SMA+ cells were shown by IF to co-express the haematopoietic marker CD34 suggesting they might be perivascular adipose tissue-derived mesenchymal progenitors. A subset of alpha-SMA+ cells also co-expressed the parathyroid marker OCM2, and the endodermic transcription factor TBX1, suggesting they might derived from chief cells through epithelial-to-mesenchymal transition. In conclusions, we identified in parathyroid neoplasia cells showing features of activated TAFs that might be involved in tumoral neangiogenesis and invasiveness.

DOI: 10.1530/endoabs.32.P525

P526

Expression of FGF23, Klotho, CaSR, and PTHrP in carcinoma in situ and germ cell tumors of the testis: implications for testicular microlithiasis

Martin Blomberg Jensen, John E Nielsen, Anne Jørgensen, Anders Juul & Ewa Rajpert-De Meyts

Growth and Reproduction, Rigshospitalet, Copenhagen, Denmark.

Introduction

Vitamin D (VD) metabolism is active in normal testis, but lost during the malignant progression from carcinoma in situ (CIS) to overt germ cell tumors (TGCTs). CIS and TGCTs are often associated with intratubular deposition of hydroxypatite (microlithiasis). Imbalance in FGF23 and PTH homeostasis may result in calcification of mesodermal-derived tissue, so we hypothesized that this mechanism may be involved in testicular microlithiasis. Here, we investigated classical regulators of VD metabolism, phosphate and calcium homeostasis: FGF23, CaSR, PTHrP, in addition to their corresponding receptors and downstream mediators in human testis, with and without CIS and TGCT.

Materials and methods

In total, 20 samples of normal adult human testis, 20 CIS, 25 TGCTs and five fetal testes were investigated by qPCR and immunohistochemistry. FGF-23 was measured with an immunoassay in serum and seminal fluid of ten patients with TGCT.

Results

Normal germ cells expressed PTHrP, PTHR, Klotho, FGFR1, FGFR3 and the phosphate transporter NPT2b, but virtually no FGF23 expression was detected. FGF23, CaSR, PTHrP and NPT2a were markedly upregulated (P < 0.05) in CIS at RNA and protein level, with a high correlation between CaSR and PTHrP (r = 0.91, P < 0.005) and a correlation of PTHrP and FGF23 with NPT2a (P < 0.01). PTHrP, but not FGF23, was expressed in fetal germ cells. The protein expression of FGF23, CaSR, and PTHrP diminished in invasive TGCTs, and FGF23 levels in serum and seminal plasma were not significantly higher in TGCTs patients compared with controls.

Conclusion

Testicular neoplasia is associated with profound changes in intratesticular VD, calcium and phosphate homeostasis. It remains to be established whether overexpression of FGF23 in CIS is a regulatory mechanism, or reflects genomic amplification associated with malignant transformation, but upregulation of FGF23 may contribute to the formation of testicular microliths in the vicinity of CIS and TGCT.

DOI: 10.1530/endoabs.32.P526

P527

The clinical characteristics of primary hyperparathyroidism (PHPT) in patients with multiple endocrine neoplasia (MEN) type 1

Liliya Rostomyan1,2, Nataliya Mokrysheva1, Anatoly Tiulpakov1, Alla Artemova1, Nataliya Kirdyankina1 & Liudmila Rozhinskaya1

Endocrine Abstracts (2013) Vol 32
Rarely PHPT could be a part of MEN 1 (2–4.5%). Little is known about clinical differences between MEN1 related and sporadic PHPT.

Aim
To compare the clinical features of PHPT in MEN type 1 cases and sporadic PHPT.

Materials and methods
Data were obtained in 442 patients: 62 sharing MEN1 phenotype (PHPT in association with pituitary adenomas and/or gastroenteropancreatic neuroendocrine tumors) (Group-I) and 380 with apparently sporadic PHPT (Group-II). Serum Ca, intact PTH, urine Ca, 25-OH-VitD, osteocalcin, β-CTXs and BMD z-score measurements, renal ultrasonography, visualization of parathyroid glands were performed in both groups. The additional diagnostic tests (prolactin levels, ultrasound of pancreas and adrenals) were performed in patients to exclude or evaluate other than PHPT endocrine disorders.

Results
The age at diagnosis was younger in Group I (39.5 (28–51) years) than in Group II (57 (48–64) years). P < 0.001. In 50% of Group I PHPT debuted before age of 40 years, whereas in Group II in 70% of patients the diagnosis was made after age of 50 years. The distribution of males/females was 1:2.6 in Group I and 2:1.0 in Group II. In 93% of Group II PHPT was caused by a single parathyroid adenoma, in Group I in 59.6% an enlargement of multiple parathyroid glands was observed. In 64% of iPTH was higher than upper normal range less than 2.5 times, whereas in Group II 54% was more than three times higher than normal limits. In the meantime the levels of Ca in both groups were not significantly different (P = 0.28). The mild PHPT was observed in Group I more frequently than in Group II (33.8 vs 19%). PHPT presented with osteoporosis with the same prevalence in both groups, but with more frequent renal manifestations in Group I. In Group I the decrease in BMD at all sites and nephrolithiasis developed independently of the degree of PTH elevation, as opposed to Group II. Multifactorial analysis revealed the combination of moderately elevated PTH and the age at diagnosis younger than 40 years to increase the risk of MEN1 related PHPT in these patients independently of their gender and the mild course of PHPT.

Conclusion
The patients with MEN1-related PHPT are younger at the diagnosis of PHPT, have more frequently multiple enlarged parathyroid glands and show mostly mild course of disease (especially in young age) and less increased PTH compared with those with sporadic PHPT.

DOI: 10.1530/endoabs.32.P527

P528
Establishment of patient-individual tumor models for endocrine tumors
Constance Hantel1, Franz Scheller1, Alexandra Ozimek2, Constanza Chiapponi2, Thomas Mussack2 & Felix Beuschlein1
1Endocrine Research Unit, Medizinische Klinik and Poliklinik IV, Ludwig-Maximilians-University, Munich, Germany; 2Department of Surgery, Ludwig-Maximilians-University, Munich, Germany.

In an attempt to amend the lack of preclinical models for endocrine tumors, we recently initiated development of patient-individual tumor models. Pieces from four adenocortical carcinomas (ACC), one aldosterone producing adenoma (APA), one pheochromocytoma (pheo), one metastasis of a malignant pheo, one adrenocortical carcinomas (ACC), one aldosterone producing adenoma (APA), one pheochromocytoma (pheo), one metastasis of a malignant pheo, one metastasis of a malignant pheo, one adrenal medullary tumor (pheo), one metastasis of a malignant pheo, one aldosterone producing adenoma (APA), one pheochromocytoma (pheo), one metabolic syndrome (Merkel cell carcinoma) were implanted subcutaneously into immunodeficient mice. CD31 analyses after tumor explantation revealed heterogeneous grades of vascularization for ACCs and NETs (from high to absent) which seemed to be overall not dependent on tumor origin. Single explants (E) showed often ki67 indices (%) and SF-1 (positive cells/six high power fields) or chromogranin A stainings (ChA morphology and stained area as % of total) comparable (P > 0.05) to the original patient tumor (ACC k67, patient: 7.9 ± 2.3, E: 8.9 ± 2.2; SF-1, patient: 4.2 ± 0.7, E: 4.2 ± 0.6; NET1 k67, patient: 7.3 ± 1.4, E: 7.7 ± 1.1; ChA, patient and E: 30–60%, nest-shaped). However, various explants revealed intra-tumoral heterogeneities maybe reflecting different regions within one patient’s tumor (ACC k67, patient: 9.7 ± 2.6 vs E1: 2.8 ± 0.9, P < 0.05; E2: 2 ± 1.2, P < 0.05; E3: 11.3 ± 3.3, P > 0.05; SF-1, patient: 3.3 ± 0.4 vs E1: 3.2 ± 0.4, P < 0.05; E2: 3.5 ± 0.1, P < 0.0001; E3: 11.2 ± 0.2, P < 0.0001; NET2 k67, patient: 2 ± 1 vs E1: 10.3 ± 0.7, P < 0.0001; E2: 7.1 ± 0.9, P < 0.001; E3: 13.1 ± 1.9, P < 0.0001; E4: 2.7 ± 0.6, P > 0.05; ChA, patient: nest-shaped: 60 ± 7.1, E1: nest-shaped: 21.9 ± 3.5; E2: 8.8 ± 2.7, nest-shaped: E3: 0 ± 2.2, diffuse; E4: 10 ± 3, diffuse; APA and pheo were low or not vascularized and ki67 indices were comparable with patient tumors (pheo, patient: 2.9 ± 0.4, E1: 2.9 ± 0.7, E2: 2.5 ± 0.6; APA, patient: 3.2 ± 0.9, E1: 1.6 ± 0.5, E2: 3.6 ± 1.7). During ongoing preclinical studies we plan to include groups with patient-tumor bearing mice to investigate putative applicability in therapeutic settings.

DOI: 10.1530/endoabs.32.P528

P529
Familial malignant paraganglioma is long-term stabilized with the tyrosine-kinase inhibitor sunitinib
Valeria Ramundo1, Francesca Marciello1, Michele Del Pretre1, Vincenzo Marotta1, Raffaella Esposito1, Anna Chiara Carratu1, Chiara di Luca di Roseto1, Annamaria Colao1 & Antongiulio Faggiano1,2
1Department of Clinical and Molecular Endocrinology and Oncology, “Federico II” University of Naples, Naples, Italy; 2Endocrinology, National Cancer Institute, “Fondazione G. Pascale”, Naples, Italy.

Introduction
Paragangliomas are neuroectodermal tumors that arise from adrenal medulla or extra-adrenal ganglia and are characterized by high vascularisation. A high rate of these tumours is genetically inherited. For malignant paragangliomas, chemo- and radiotherapy are potentially effective, but tumor response is of short duration and patient prognosis is quite poor. Sunitinib is a tyrosine-kinase inhibitor, targeting VEGFR1,-2, PDGFRα, -β, RET and c-KIT.

Recent experiences highlighted that sunitinib is potentially effective in patients with malignant paraganglioma. Our data aim to suggest a long-term use of sunitinib to arrest progression in familial paragangliomas.

Case report
Two patients (female, 48 years; male, 27 years) affected with persistent post-surgical malignant abdominal paraganglioma associated with paragangliomatosis type 4 (SDHH mutations) were treated with sunitinib 37.5 mg/day. One of them experienced a partial response and one another a tumour stabilisation. At the last evaluation, 42 months after starting sunitinib, biochemical parameters (24-hour urine catecholamines and metanephrines) were in the normality range and tumor lesions were stable. Sunitinib was well tolerated and no serious adverse event was observed in both patients.

Conclusions
Sunitinib seems to be an effective agent for the management of patients with unresectable/advanced familial malignant paragangliomas. The striking finding of this report is that sunitinib at the dose of 37.5 mg/day is able to obtain long-time stabilization of tumor progression.

DOI: 10.1530/endoabs.32.P529

P530
Insulinoma: is enucleation a safe option?
Anneke Jilesen, Heinz-Josef Klumpen, Peter Bisschop, Olivier Busch, Thomas van Gulik, Dirk Gouma & Els Nieveen van Dijkum
AMC, Amsterdam, The Netherlands.

Background
Insulinomas are the most prevalent functional neuroendocrine tumors of the pancreas. Enucleation is often preferred to pancreatic resection because it’s minimally invasive nature. The aim of this study is to assess the post-operative surgical outcome in particular pancreatic fistula after resection.

Methods
All patients with insulinomas were selected from a retrospective database of resected pancreatic neuroendocrine tumors (pNET). Patients were operated between 1992 and 2012. Surgical procedure and post-operative outcome were analysed.

Results
A total of 109 patients with pNET underwent resection, 22 patients had an insulinomas (20%), 12 women and ten men with a median age of 50 years (21–83 years). Three patients had MEN-1 syndrome (1%). Somatostatin receptor scintigraphy was performed in 12/22 patients and showed accumulation of the radiopharmacon in the insulinomas in two patients. Twelve patients underwent enucleation of the insulinoma, n = 8 located in the head, n = 2 in the tail, n = 2 in the central/tail region. All enucleated insulinomas were smaller than 20 mm. Ten patients underwent pancreatic resection, n = 6 tail resection, n = 3 corpus/tail resection, n = 1 head/corpus resection including pancreatic jejunostomy.
Complications occurred in 7/12 (58%) enucleation patients and in 4/10 (40%) patients with a pancreatic resection (P=0.4). The most frequent complication was pancreatic leakage in 9/22 (41%), respectively 7/12 for enucleation and 2/10 for pancreatic resection (P>0.1). Two patients developed diabetes mellitus post-operatively; both patients were diagnosed with recurrent insulinoma and underwent multiple pancreatic resections. One MEN-1 patient developed metastatic disease of the insulinoma after resection of the primary.

Conclusions
Enucleation can be frequently performed in 55% for insulinomas and it’s a less invasive operation technique without endocrine insufficiency but with a high complication rate, especially for pancreatic fistula. Although insulinomas are usually small, a pancreatic resection is a safe alternative option. Careful patient selection and operation should be performed.

DOI: 10.1530/endoabs.32.P530

PS31
Long-term outcome after transarterial chemoembolization of hepatic metastases from neuroendocrine tumors
Sanja Ognjanovic1, Milan Petakov1, Tatjana Isailovic1, Valentina Elezovic1, Djuro Macut1, Bojana Popovic1, Ivana Bozic1, Tamara Bogavac1, Dusan Ilic1, Moncolj Colic1,2 & Svetozar Damjanovic1
1Clinic for Endocrinology, Diabetes and Metabolic Diseases, Belgrade, Serbia; 2Centre for Radiology, Clinical Centre of Serbia, Belgrade, Serbia.

Introduction
Most patients with neuroendocrine tumors (NETs) present with liver involvement at the time of diagnosis. Trans-catheter arterial chemoembolization (TACE) is accepted treatment of patients with non-resectable hepatic metastases from NETs.

Aim
To analyze objective tumor response and clinical outcome in patients with hepatic metastases from NETs who underwent TACE.

Methods
Thirty-one patients underwent 140 TACE procedures. Kaplan–Meier method was used to calculate the progression-free survival (PFS) and overall survival (OS). Tumor responses were measured by CT and MRI, and were assessed using the RECIST criteria.

Results
NET originated from the pancreas (n=5), small bowel (n=11), colon (n=1), lung (n=5), unknown primary localization (n=9). Almost all patients (93.5%) had received medical treatment including octreotide, interferon-α, chemotherapy, and peptide-receptor-radiolucine therapy. According to WHO criteria, majority were well-differentiated neuroendocrine carcinomas (71.4%). Median OS for all NETs was 59 months (4–180) with 5-year survival of 58.9%. The 5-year OS rates for patients with pancreatic, carcinoid and unknown primary tumors were 33.3, 75 and 38.9% respectively. Median PFS for all patients was 32 months (1–139). The only group of patients with 5-year PFS was the one with carcinoid tumor (59.3%). None of the 31 patients had complete response. After third TACE a partial response was observed in two, stable disease in eight patients and there was none of the patients with the progressive disease. After the fifth TACE partial response was observed in three, stable disease in five and progressive disease in four patients.

Conclusion
The OS after TACE for all NETs is approximately 5 years, and median time to progression is about 32 month. Patients with carcinoid tumors had better outcomes than others. TACE is effective in stabilization and reduction of tumor growth in patients with hepatic metastasis from NETs.

DOI: 10.1530/endoabs.32.P531

PS32
Pituitary transforming gene 1 (PTTG1) expression in seminoma
Domenico Milardi1, Giuseppe Grande2, Francesco Pierconti3, Maurizio Martin2, Tonia Cenci3, Gaetano Gulino4, Giovanni Schinzari5, Laura De Marinis2
3Department of Pathology, Catholic University of Sacred Heart, Rome, Italy; 4Department of Pathology, Catholic University of the Sacred Heart, Rome, Italy; 5Department of Internal Medicine, Unit of Medical Oncology, Catholic University of Sacred Heart, Rome, Italy; 2Department of Urology, Catholic University of the Sacred Heart, Rome, Italy; 1International Scientific Institute “Paolo VI”, Catholic University of the Sacred Heart, Rome, Italy; 2Department of Clinical Medicine, Unit of Endocrinology, Catholic University of the Sacred Heart, Rome, Italy; 3Department of Pathology, Catholic University of Sacred Heart, Rome, Italy; 4Department of Radiology, Catholic University of Sacred Heart, Rome, Italy; 5Department of Medical Oncology, Catholic University of Sacred Heart, Rome, Italy.

PTTG1-expression in neoplastic cells in the front of the tumor infiltration and in peripheral area, with a greater number of positive cells in the borders of the tumor and gradient periphery/center significantly correlate with the size of the tumor. PTTG1 positive staining was also reported in the periportal region a nuclear staining prevalent pattern.

We firstly described neoplastic PTTG1-positive cells with nuclear and cytoplasmatic staining in seminoma. Our distribution data support the idea that PTTG1-expression in neoplastic cells in the front of the tumor infiltration and in the intertubar areas might respond to demand of the tumor cells to move and invade surrounding tissue, increasing tumor angiogenesis. Further investigation is required to clarify if a functional abrogation of PTTG1 could provide new therapeutic approaches in the management of seminoma.

DOI: 10.1530/endoabs.32.P532

PS33
Polymorphisms of the glucocorticoid receptor gene, as phenotype modifiers in patients with hormonally inactive adrenal adenomas
Bence Acz1,2, Agnes Szappanos2, Karolina Feldman-Kovacs2, Istvan Liko2, Judit Majnik2, Orosolya Acz3, Nikolette Szucs3, Miklos Toth3, Karoly Racz2 & Attila Patocs1,3
1Semmelweis University School of Ph.D. Studies, Budapest, Hungary; 22nd Department of Internal Medicine, Semmelweis University, Budapest, Hungary; 3Gedeon Richter Ltd., Budapest, Hungary; 42nd Department of Internal Medicine and of Laboratory Medicine, Semmelweis University, Budapest, Hungary; 5Molecular Medicine Research Group, Hungarian Academy of Sciences, Budapest, Hungary.

Introduction
Altered sensitivity against glucocorticoids is partly influenced by polymorphisms (SNP) of the glucocorticoid receptor gene (GR). The aim of the present study was to extend our earlier study by inclusion and evaluation the role of the Bcll and A3669G polymorphisms of the GR in patients with hormonally inactive adrenal adenomas.

Description of methods
This is a retrospective, single-centre genetic association study. The study included 99 patients with hormonally inactive (HI) adrenal adenomas discovered incidentally (incidentalomas) and 129 healthy controls. Hormonal evaluation of the hypothalamus–pituitary–adrenal axis, measurement of metabolic parameters was carried out in patients, and genetic analysis in all subjects. The Bcll polymorphism was detected by allele specific PCR while the A3669G was detected by allele specific PCR.

Results
The prevalence of the Bcll was lower in unilateral while the prevalence of the A3669G was lower in patients with bilateral HI than in healthy controls, (Bcll: 21.8 vs 34.5%; A3669G: 10.8 vs 22.1% P<0.05). Patients who carried the Bcll polymorphism had higher: systolic blood pressure, BMI, serum cholesterol level and ACTH level measured after methyprylon test. The prevalence of obesity was also higher in Bcll carriers, and this prevalence further increased when the A3669G SNP was present. Although lower prevalence of hyperlipidemia and plasma ACTH level was detected in the same group.

Conclusion
Our results confirm that besides the development of adrenal tumors special in bilateral cases the polymorphic allele of the N363S and the wild type alleles of the Bcll and A3669G represent genetic risk factors. Different mechanisms related to GR genetic variants alone or together may contribute to the morbidity found in these patients.

DOI: 10.1530/endoabs.32.P533
Mutations in the mitochondrial succinate dehydrogenase (SDH) subunits A, B, C, and D have been shown to hamper oxidative phosphorylation and predispose to pheochromocytomas (PHEOs) and parangangliomas (PGLs). These tumors are characterized by a glycolytic and pseudohypoxic phenotype, which is also seen in most PHEOs/PGLs occurring as part of von Hippel–Lindau (VHL) syndrome, due to VHL gene mutations. The rate of extra-adrenal tumor origin and malignancy however is particularly high in SDHB-PHEOs/PGLs, while VHL-PHEOs/PGLs are almost always adrenal and benign.

We have recently shown that despite decreased complex II activity, mRNA and protein abundance of several oxidative phosphorylation subunits is elevated in SDHB compared to VHL-PHEOs/PGLs. Here we present ultrastructural evidence for vast differences in number and appearance of mitochondria in SDHB and VHL derived PHEOs/PGLs, as we have previously presented on a smaller patient cohort. Forty-three tissue samples of SDH (47% metastatic) and VHL patients (0% metastatic) have been evaluated. In SDHB, PHEOs/PGLs density and size of mitochondria was increased compared to VHL-PHEOs/PGLs with a disrupted cristae structure in both types of PHEOs/PGLs. Western blot for the mitochondrial marker cytochrome C revealed higher levels in SDHB-PHEOs/PGLs. No difference was observed between metastatic and non-metastatic SDHB tumors.

Our data indicates that disruption of the respiratory chain caused by SDHB mutations may lead to an accumulation of aberrant, possibly dysfunctional mitochondria. Further studies on live cells are mandated to conclude if the disrupted appearance of the mitochondria leads to a loss of mitochondrial membrane potential and functionality or reactive oxygen species generation and the potential role of aberrant mitochondria in metastatic potential.

DO: 10.1530/endoabs.32.P534

**P535**

Adrenal lesions in patients with neuroendocrine tumors

Bojana Popovic1, Djuro Macun1, Milan Petakos2, Ivana Bozic1, Tamara Bogavac1, Tatjana Isailovic1, Sanja Oggnajnovic1, Valentina Elezovic1, Marjan Micev2, Nemanja Menkovic3, Dusan Ilic1 & Svetozar Damjanovic1

1Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Centre of Serbia, Belgrade, Serbia; 2Clinic for Gastroenterology, Gastroenterology, Pathohistology Unit, Clinical Centre of Serbia, Belgrade, Serbia; 3Centre for Radiology, Clinical Centre of Serbia, Belgrade, Serbia.

**Introduction**

The coexistence of adrenal tumors (AT) in patients with neuroendocrine tumors (NETs) has not been extensively studied. The aim of our study was to investigate their prevalence and clinical significance in these patients.

**Materials and methods**

We retrospectively studied 447 patients with NETs of all localizations, treated at our department between 2004 and 2012. Diagnosis was established pathohistologically, classification performed according to stage and grade as proposed by ENETS, and disease progression monitored by CT/MRI imaging. The nature of AT was evaluated pathohistologically when possible, or by CT/MRI characteristics indicative of metastatic or non-metastatic lesion. Functional status was assessed appropriately in all patients. Statistical analysis was performed by SPSS software.

**Results**

The prevalence of ATs was 14.3% (64 patients). The involvement was unilateral in 56.4% (42.2% left and 15.6% right adrenal) and bilateral in 40.6% of patients, with mean diameter of 30.2±20.9 mm (9–108 mm). The majority of patients had primary pancreatic NET (40.6%), followed by lung NET (28.1%), NET of unknown primary (9.4%) and intestinal NET (7.9%), while other localizations were present with less than 4.7% each. Ten patients (15.6%) had MEN1 syndrome. Metastatic nature was pathohistologically verified or was indicative by CT/MRI characteristics in majority of cases (55.6%, 35 patients), five of which (14.3%) had MEN1. Out of the remaining 29 patients with benign lesions (6.5% of all patients with NETs), size progression was noted in only one AT, and only one tumor was functionally active (subclinical Cushing’s syndrome). Adrenal involvement positively correlated with tumor grade (r=0.389, P<0.001) and stage (r=0.261, P=0.007). Overall survival of patients with coexistent AT was 77.0 months (95% CI 23.9–130.1), which was not significantly different than OS of patients without AT (P>0.05).

**Conclusion**

Adrenal tumors in our group of patients with NETs were mostly metastatic, but their overall clinical relevance needs further studies.

DOI: 10.1530/endoabs.32.P535

---

**P536**

Association between expression of Ki-67, parafibromin, p27, and Rb protein and the biological behavior in parathyroid tumors

Keiko Ohkawa, Chie Masaki, Junko Akaiishi, Akifumi Suzuki, Takashi Uruno, Hiroshi Shibuya, Wataru Kitagawa, Mitsuji Nagahama, Kiminori Sugino & Koichi Ito

1Department of Internal Medicine, School of Medicine of Ribeirao Preto, University of Sao Paulo, Ribeirao Preto, Sao Paulo, Brazil; 2Department of Pathology, School of Medicine of Ribeirao Preto, University of Sao Paulo, Ribeirao Preto, Sao Paulo, Brazil; 3Department of Surgery and Anatomy, School of Medicine of Ribeirao Preto, University of Sao Paulo, Ribeirao Preto, Sao Paulo, Brazil.

**Introduction**

Parathyroid carcinoma (PC) is uncommon and occurs in only 1–5% cases of primary hyperparathyroidism. The histological diagnosis of parathyroid tumors can be challenging, and beneficial histological markers are not available for diagnosis or predicting the prognosis of patients. In this study, we investigated the expression of Ki-67, parafibromin, p27, and Rb protein in parathyroid tumors and assessed the correlation between histological diagnosis or prognosis, by using immunohistochemical staining in patients with confirmed PC and parathyroid adenoma.

**Methods**

Thirty-eight formalin-fixed, paraffin-embedded tissue samples of surgically resected PC (n=18) and parathyroid adenoma (n=20) were studied by immunohistochemical analysis for Ki-67, parafibromin, p27, and Rb expression.

**Results**

Positive findings were noted for Ki-67 in 11 (61.1%) cases of carcinoma and none of the cases of adenoma (P=0.0002), for parafibromin in one (5.6%) case of carcinoma and 19 (95%) cases of adenoma (P<0.0001), for p27 in three (16.7%) cases of carcinoma and all cases of adenoma (P<0.0001), and for Rb in one (5.6%) case of carcinoma and 13 (65.0%) cases of adenoma (P<0.0001). Furthermore, the high rate of Ki-67 expression and the weak immunoreactive expression of parafibromin, p27, and Rb may indicate poor prognosis of PC. These results indicate that the use of Ki-67, parafibromin, p27, and Rb may be helpful in the assessment of parathyroid tumors. Furthermore, the high rate of Ki-67 expression and the weak immunoreactive expression of parafibromin, p27, and Rb may indicate poor prognosis of PC.

**Conclusions**

These results suggest that Ki-67, parafibromin, p27, and Rb expression may be helpful markers for diagnosis and predicting the clinical outcome of patients with PC.

DOI: 10.1530/endoabs.32.P536

---

**P537**

**RPS13 and cell cycle signaling pathways in pituitary tumorigenesis**

Claraia Martins1, Renata Camargo2, Fabiano Saggioro3, Luciano Neder 3, Helio Machado4, Aytron Moreira & Margaret Castro5

1Department of Internal Medicine, School of Medicine of Ribeirao Preto, University of Sao Paulo, Ribeirao Preto, Sao Paulo, Brazil; 2Department of Physiology, School of Medicine of Ribeirao Preto, University of Sao Paulo, Ribeirao Preto, Sao Paulo, Brazil; 3Department of Pathology, School of Medicine of Ribeirao Preto, University of Sao Paulo, Ribeirao Preto, Sao Paulo, Brazil; 4Department of Surgery and Anatomy, School of Medicine of Ribeirao Preto, University of Sao Paulo, Ribeirao Preto, Sao Paulo, Brazil.

**Introduction**

Abnormalities in cell cycle pathways, such as CDKINB (p27) underexpression, have been identified in the pathogenesis of pituitary adenomas, but their underlying mechanisms have not been elucidated. Ribosomal proteins have been recently related to pituitary tumorigenesis. In gastric cancer, RPS13 down-regulates p27 and promotes cell cycle progression; these mechanisms have not yet been explored in pituitary adenomas.
Objective
To evaluate the relationship between RPS13 and CDKN1B, CDK2, CCNE1, MYC gene expression in pituitary tumorigenesis and its association to clinical findings.

Methods
We studied four groups: non-functioning pituitary adenomas (NFPA, n=21), GH-secreting adenomas (n=18), ACTH-secreting adenomas (n=12) and normal pituitaries (n=20). Clinical and pathological data were collected. RNA was isolated by TRIzol method. Gene expression was assessed by qRT-PCR. Kruskal-Wallis test was used for continuous variables between groups and Fisher Exact test for categorical data.

Results
Differential gene expression among the groups were observed in CDKN1B (P=0.03), CCNE1 (P=0.02) and MYC (P=0.002), but not RPS13 (P=0.1) and CDK2 (P=0.07). We observed CDKN1B underexpression in somatotrophinomas, CCNE1 overexpression in NFPA and MYC underexpression in NFPA. In corticotrophinomas, we found no association between gene expression and tumor size, remission or immunohistochemistry (IHC). In somatotrophinomas, no relationship was found between gene expression and tumor size, visual field, IGF-1 levels, basal and post-oGTT GH levels, IHC, post-surgery remission and disease control. Tumors with higher CDKN1B expression tended to achieve control with somatostatin agonist (P=0.08). In NFPA, higher CDK2 expression was associated to null cell subtype (P=0.03) with a tendency to correlate with tumor size (P=0.08). Higher CCNE1 expression was associated with remission (P=0.02).

Conclusion
The p27-CDK2-CCNE1 pathway seems dysregulated in pituitary adenomas and does not seem to be the underlying mechanism. Overexpression of p27, however, does not seem to be the underlying mechanism.

DOI: 10.1530/endoabs.32.P538

P539
Involvement of PKCβ and PKCδ isoforms in TSH signaling pathway in thyroid cancer cell lines
Daniela Molé1, Erica Gentilin1,2, Teresa Gagliano1, Federico Tagliati1, Ettore degli Uberti1,2 & Maria Chiara Zatelli1,2
1Section of Endocrinology, University of Ferrara, Ferrara, Italy; 2Laboratorio in rete del Tecnopolo “Tecnologie delle terapie avanzate” (LTTA) of the University of Ferrara, Ferrara, Italy.

It is well established that most TSH effects on the thyroid gland, including stimulation of proliferation, thyroid hormone synthesis and expression of thyroid-specific genes, are transmitted mainly by the adenylyl cyclase pathway. However, in human follicular cells and in rat FRTL-5 cells, TSH can also stimulate the β isoforms of PLC that catalyzes the hydrolysis of phosphatidylinositol 4,5-phosphate, yielding the second messengers DAG and inositol 1,4,5-phosphate facilitating an increase in intracellular Ca2+. In FRTL-5 cells TSH has been suggested to increase DAG via phospholipase D, which produces DAG from phosphatidylincholine hydrolysis, suggesting an alternative mechanism for TSH-dependent activation through protein kinase C (PKC).

In the present study, we characterize the PKCβ and PKCδ isoforms expression and function in human follicular carcinoma cells, FTC133, and in human transformed thyrocytes, Nthy-ori cells, in order to understand whether these PKC isoforms are involved in TSH-mediated follicular cell proliferation and apoptosis. We mainly focus on PKCβ and PKCδ isoenzymes which are the most abundantly expressed isoforms in several tissues, are the most extensively studied and have two opposing roles in regulating cell proliferation. In the Nthy-ori cells TSH stimulated cell proliferation and protected from apoptosis with a PKC-mediated mechanism. At the contrary, TSH did not increase FTC133 cell viability nor protected the cells from PKC- inhibitor induced apoptosis. However, in FTC133 cells TSH induced PKC expression, as well as downstream PKC targets GSK3β and AKT phosphorylation through a PKC-mediated mechanism. Moreover, immunofluorescence showed PKCβ and PKCδ perinuclear and citosolic location. These data suggest that TSH plays different roles in normal vs neoplastic thyrocytes.

Further studies are needed to clarify the role of PKCβ and PKCδ in the TSH signaling pathway in thyroid cells.

DOI: 10.1530/endoabs.32.P539

P540
PKCδ plays an important role in regulating human medullary thyroid carcinoma cell viability
Daniela Molé1, Erica Gentilin1,2, Teresa Gagliano1, Federico Tagliati1, Maria Rosaria Ambrosio1, Ettore degli Uberti1,2 & Maria Chiara Zatelli1,2
1Section of Endocrinology, University of Ferrara, Ferrara, Italy; 2Laboratorio in rete del Tecnopolo “Tecnologie delle terapie avanzate” (LTTA) of the University of Ferrara, Ferrara, Italy.

Protein kinase C (PKC) is a family of serine-threonine kinases that regulate many cellular processes including proliferation and survival. Previous evidence has shown that PKCδ is involved in the control of human medullary thyroid carcinoma (MTC) proliferation and survival by modulating apoptosis, with a mechanism that implicates PKCδIII isofrom and translocation in different subcellular compartments.

In this study, we investigated the role of PKCδ signaling in the proliferation of a human MTC cell line, the TT cells. We found that pharmacological inhibition of the PKCδ pathway with Rottlerin reduces caspase 3/7 activity. Using a shRNA vector system, which provides more than 90% gene expression inhibition, we found that cell proliferation is greater in PKCδ-defective TT cells than in mock-transfected cells, this difference being significant after 3 days. In addition, we found that PKCδ silencing reduces STAT5c/Y994(699) phosphorylation but not AKT/Thr473 and p70S6K(T389) phosphorylation, all downstream targets of PKCδ pathway involved in cell growth, cell cycle and proliferation. Moreover, we demonstrated that PKCδ silencing increased human VEGF secretion after 4 days.

These observations indicate for the first time that PKCδ pathway plays an important role in the growth control and VEGF secretion of human MTC cells.

Key words
PKCδ, cell viability, TT cell lines

DOI: 10.1530/endoabs.32.P540

Endocrine Abstracts (2013) Vol 32
**P541**

**Sequential use of the kinase-inhibitors sorafenib and sunitinib in a patient affected with pluri-metastic iodine-refractory follicular thyroid carcinoma**

Vincenzo Marotta1, Valeria Ramundo1, Francesca Marcilli1, Michela Del Prete1, Antonella Di Sarro2, Raffaella Esposito3, Annachiara Carratù1, Chiara de Luca di Roseto1, Luigi Camera1, Annamaria Colao1 & Antongiulio Faggiano1

1Department of Molecular and Clinical Endocrinology and Oncology, Federico II University, Naples, Italy; 2IX Infectious Disease and Interventional Ultrasound Unit, “D. Cotugno” Hospital, Naples, Italy; 3Department of Biomorphological and Functional Sciences, Federico II University, Naples, Italy; 4Endocrinology, National Cancer Institute, “Fondazione G. Pascale”, Naples, Italy.

Introduction
Kinase-inhibitors (KIs) are effective for treatment of most aggressive endocrine cancers. The crucial point about treatment with KIs is that these agents are not curative and their effects are at best transitory and are always followed by a restoration of tumour growth and progression. Several retrospective and phase II studies demonstrated efficacy of both sorafenib and sunitinib for treatment of iodine refractory differentiated thyroid cancer although results from phase III trials are not available yet.

Case report
A 57 year old woman was affected with a pluri-metastic iodine refractory follicular thyroid carcinoma. She presented multiple metastases in lymph nodes (both cervical and mediastinal), lung, liver, bone. Treatment with sorafenib was started and a radiological response was achieved (stable disease according to RECIST criteria). Nevertheless, effectiveness of sorafenib was not durable: progression of disease was restored after 7 months of treatment. Then treatment with sunitinib was started. Interestingly, sunitinib obtained a clear morphological regression of disease (partial response according to RECIST). At present, patient is receiving combination treatment with sunitinib (lasting for 11 months) is still ongoing and disease is still not progressive.

Conclusions
KIs may lead to arrest of tumour progression and improvement of survival. However, disease is expected to escape during therapy. For this reason, to identify a therapeutic scheme based on a sequential use of different KIs could delay the development of tumor progression.

DOI: 10.1530/endoabs.32.P541

**P542**

**Endogenous Cushing’s syndrome: the Filipino clinical experience of 19 cases**

Tom Edward Lo, Joyce Cabradilla & Cecilia Jimeno

University of the Philippines, Philippine General Hospital, Manila, The Philippines.

Background and significance
Endogenous Cushing’s syndrome is a rare disease entity approximately 13 cases per million population. In Asia, and specifically in the Philippines incidence is unknown. As well, it’s a clinical presentation among Filipinos is not well described. The local epidemiology of obesity, diabetes and hypertension are different from other countries. These conditions are the usual initial differential diagnosis for Cushing’s syndrome. This report on a collection is thus important for the awareness of clinicians on the clinical presentation and course of individuals with this condition.

Methodology
Medical records of patients diagnosed with Cushing’s syndrome within the year 2005–2011 were retrieved using the ICD-10 code for Cushing’s syndrome (E24). All selected medical records were individually reviewed, assessed and carefully recorded.

Results
The study included 19 cases (eight pituitary adenoma, seven adrenal adenoma, four ectopic adrenomas) of endogenous Cushing’s syndrome. Female predominance was noted. The most commonly reported clinical symptom and sign were weight gain and moon facies respectively. Short clinical course, hyperpigmentation, ecchymoses, behavioral changes and severe hypokalemia were observed to be more prominent among cases with ectopic sources. All cases had significantly elevated midnight serum cortisol level and 24 h urine cortisol with ectopic sources exhibiting the highest level. There was no observed correlation between the tumour size and level of serum cortisol in all types. Majority underwent tumour resection leading to complete reversal of steroid excess.

Conclusion
Adrenal, pituitary and ectopic foci are the main sources of endogenous steroid excess. Ectopic ACTH syndrome manifests differently with other causes providing clues that might help in rapid clinical differentiation. Imaging studies should only be used to confirm tumour location after rigorous biochemical tests. Surgical management remains to be the definitive cure for most of the cases, hence prompt diagnosis and localization is necessary.

DOI: 10.1530/endoabs.32.P542

**P543**

**Hyperparathyroid jaw tumour syndrome**

Pranav Kumar & Keston Jones
Singleton Hospital, Swansea, UK.

Hyperparathyroid jaw tumour syndrome is a familial form of primary hyperparathyroidism. Individuals are predisposed to develop parathyroid carcinomas (15%), ossifying fibromas of mandible and maxilla (30%), renal abnormalities including cystic lesions and hamartomas, and uterine tumours (1,2).

The pathogenic mutation is in CDC73 gene (previously known as HRPT2 and Clor28) inherited in an autosomal dominant manner.

Our patient was the first person in the UK to have the diagnosis confirmed on genetic testing. Two sisters had primary hyperparathyroidism. Father had hyperparathyroidism and an ossifying fibroma. During subsequent follow up, she was found to have a small neuroendocrine tumour of her pancreas and is under regular review. The proposed screening protocol is discussed.

References

DOI: 10.1530/endoabs.32.P543

**P544**

**Multimodal combination of interferon and loco-regional treatment for disease control in progressive metastatic pheochromocytoma/paraganglioma patients**

Julien Hadoux, Désirée Daudréis, Caroline Caramella, Sophie Leboulleux, Abir Al Ghual, Cécile Chougnet, Frédéric Dumont, Frédéric Deschamps, Martin Schlumberger & Eric Baudin

Institut Gustave Roussy, Villejuif, France.

Interferon-α (IFN-α) has shown some activity in neuroendocrine tumors with disease stabilizations. Malignant pheochromocytoma and paragangliomas (MPGGL)s have a heterogeneous behavior with a slow progression rate, most of the time and a high frequency of bone metastases. Stabilizing disease and preventing skeletal-related events are two goals to achieve in the management of MPGGLs patients.

This retrospective study evaluated a multimodal strategy of IFN-α combined to loco-regional treatments (LRT) (radiation and/or interventional radiology and/or surgery) for disease control in patients with progressive MPGGLs. Progression free survival (PFS) was primary endpoint; response rate, safety and symptomatic efficacy were secondary endpoints.

Eleven consecutive patients received peg-IFN-α 2A (90–180 μg/week) or IFN-α 2B (1.5–3 MU×3/week) at our institution between December 2005 and May 2010 as first (n=3), second (n=5) or subsequent line (n=3) of treatment. Six patients were men (55%); median age was 41. At the beginning of treatment, ten patients had progressive disease demonstrated by PET scan (n=8), MIBG (n=3) or CT-scan (n=2); data were missing for one patient. Nine patients had bone-predominant disease (bone-only, n=4). During IFN-α therapy, a mean number of 3 (range 1–8) bone directed LRT were performed. Most frequent all grade IFN-α-related toxicities were asthenia (n=9), anemia (n=5), lymphopenia (n=5), diarrhea (n=5). One patient had cardiac arrest while on therapy and survived. Symptomatic relief of pain, headaches, diarrhea or sweating occurred in 43% of seven symptomatic patients. Response was evaluable in ten patients: one partial response, eight stable diseases and one progressive disease (PERCIST or RECIST1.1) were seen. With a median follow up of 54 months, median overall survival was not reached and median PFS was 14.4 months.

This study demonstrates the symptomatic and stabilizing effect of a multimodal treatment combination of IFN-α and LRT in progressive metastatic PPGLs.

DOI: 10.1530/endoabs.32.P544
**P545**

**The metabolic complications in adrenal tumors: a retrospective study in 56 patients**

Catalina Poiana1,2, Mara Carosote1,2, Dan Hortopan2, Cristina Corneci2, Adriana Groza1, Raluca Trifanescu1,2, Bogdan Stănescu1,2 & Diana Paun1,2

1Davila UMF, Bucharest, Romania; 2Parhon Institute, Bucharest, Romania; 3Medlife, Bucharest, Romania.

Introduction

The metabolic complications in adrenal tumors, regardless secretor or not, are a common finding, thus representing a supplementary warning in these patients related to the non-endocrine therapy as anti-hypertensives, or hypolipemiants drugs, etc.

Aim

We analyze the frequency of metabolic complications in primitive adrenal tumors.

Materials and methods

This is a retrospective study in patients diagnosed with adrenal tumors (secretor or non-secretor tumors). The patients with Cushing’s disease were not included, regardless the adrenal aspect. The historical confirmation was obtained in all the secretor cases and only in 19% of non-secretor adrenal tumors (incidentalomas) where surgery was not performed. This is a retrospective study.

Results

Fifty-six patients were registered. 14.28% of cases had bilateral tumors. The mean age was 48.2 years. 12.5% of patients were men. 8.9% of patients had adrenal Cushing. 12.5% had pheochromocytoma. 14.25% had melanoma. The others had rare diagnosis as gangliocytoma or schwannoma. All the patients with pheochromocytoma and adrenal Cushing had different types of arterial high blood pressure and 56.2% of the patients with incidentalomas (essential hypertension). 60% of patients with adrenal Cushing had diabetes mellitus, 28.57% of those with pheochromocytoma, and 21.8% of those with incidentalomas. 80% of patients with adrenal Cushing were non-normal weighted. 65.62% of the patients with non-secretor adrenal tumors were obese or over-weighted. 80% of patients with Cushing syndrome had high blood cholesterol, and 42.85% of those with pheochromocytoma, and 46.67% of those with incidentalomas. We found no correlations between the metabolic component and the tumor size as pointed by computed-tomography, or the hormonal levels in secretor tumors.

Conclusion

In our study, the metabolic complications were found in more than half of the patients, regardless the secretor profile but the relationship to the adrenal hormones production is not presented in non-secretor tumors, thus an essential overlapping component as metabolic syndrome is associated.

DOI: 10.1530/endoabs.32.P545

**P546**

**Malignant melanoma and prolactine imbalance**

Corina-Daniela Nicolae1,2, Illica Nicolae2, Andra Caragheorgheopol1, Sorina Schipor1, Silvia Alecu1 & Mihail Alecu1

1University of Medicine and Pharmacy Carol Davila, Bucharest, Romania; 2Victor Babes Hospital of Tropical and Infectious Diseases, Bucharest, Romania; 3National Institute of Endocrinology C.I. Parhon, Bucharest, Romania; 4Carol Davila National Hospital of Nephrology, Bucharest, Romania.

Introduction

Malignant melanoma is a challenging illness for researchers due to unknown hormonal disorders involved in promoting/developing this disease. Some authors accept nowadays, that prolactin is involved in extrapituitary carcinogenesis. The authors aimed to study the status of prolactin in patients with melanocytic lesions and the impact of surgical removal on prolactinemia.

Method

The study included 128 adults with melanoma and 48 with dysplastic nevi. All the patients were evaluated before, and after surgical removal of the tumor. The control group involved 48 healthy participants. All the groups were homogenous for age and sex.

Prolactin (chemiluminescent method by access immunoassay systems) was evaluated at diagnosis (preoperative) and 8 weeks after surgical removal.

Results

High levels of prolactin were determined in patients with melanoma comparative with prolactin in patients with dysplastic nevi (10.55±8.50 vs 5.94±2.87 ng/ml 95% CI, P < 0.01) and in the control group (10.55±8.50 vs 5.74±3.60 ng/ml, 95% CI, P < 0.01). The statistical analysis showed no significant correlations between prolactin variation and tumor characteristics (site tumor, histological type, presence/absence of ulceration, Clark level, Breslow index).

Prolactin variation before and after the surgical removal was statistically significant (10.55±8.50 vs 9.23±5.43 ng/ml 95% CI, P < 0.01), while prolactin did not vary significantly in dysplastic nevi group.

Conclusions

High levels of prolactin were detected in patients with melanoma, levels that decreased after surgical removal of tumor. These results sustain the idea that prolactin is an active participant in tumor development. The data of our study could permit the development of new therapeutic targets that can block the effect of prolactin by decreasing the local production of prolactin, or by blocking its receptors.

DOI: 10.1530/endoabs.32.P546

**P547**

**Influence of iron deficiency on angiogenesis in melanoma patients**

Illica Nicolae1, Corina-Daniela Nicolae1, Sorina Schipor1 & Andra Caragheorgheopol1

1Victor Babes Hospital of Tropical and Infectious Diseases, Bucharest, Romania; 2University of Medicine and Pharmacy Carol Davila, Bucharest, Romania; 3National Institute of Endocrinology C.I. Parhon, Bucharest, Romania.

Introduction

Iron deficiency contributes to stabilization of HIF1α and upregulation of genes that stimulate angiogenesis in diseases associated with oxidative stress. The authors’ interest is centered on evaluation of the relation between iron status and angiogenesis (VEGF-A, sVEGFR) in patients with melanoma.

Methods

The study included 128 patients with melanoma before surgical removal of the tumor. We determined ferritin (immunoturbidimetric method), sideremia (spectrophotometric method), transferrin (immunoturbidimetric method), transferrin saturation coefficient for evaluating iron status in organism, and, VEGF-A, VEGF-R (ELISA method) for evaluating angiogenesis.

Results

Iron deficiency was identified in 31 (24.2%) melanoma patients and was defined as follows: sideremia <30 µg/dl, ferritin <20 µg/ml, transferrin saturation coefficient <15%. The authors observed no changes of iron status in 85 (66.4%) melanoma patients. Iron overload, serum iron >150 µg/dl, ferritin >200 ng/ml, transferrin saturation coefficient >50%, was identified in 12 (9.3%) melanoma patients.

The statistical analysis showed a strong correlation between ferritin level and VEGF: r = 0.823, IC95% = 0.95%, P < 0.001, between ferritin level and sVEGFR1: VEGF-A ratio: r = -0.362, IC95% = 0.95%, P < 0.05 in melanoma patients with iron deficiency. This relation was not observed for other studied situations (melanoma patients with normal status of iron or iron overload).

Conclusions

Low serum levels of iron were associated with high concentrations of proangiogenic mediators (sVEGFR and VEGF-A) in melanoma patients, factor that could increase tumor angiogenesis.

DOI: 10.1530/endoabs.32.P547

**P548**

**Calcitonin comparison study of LIAISON XL vs IMMULITE 2000**

Mira Manor & Yizhak Mayer

Clalit Health Care, Tel Aviv, Israel.

Introduction

Automated calcitonin assays are one-step sandwich chemiluminescence immunoassay, intended for the quantitative determination of calcitonin in human serum. Calcitonin is the most specific and sensitive marker of medullar thyroid carcinoma for both primary diagnosis and the post-surgical follow-up. Recently a new fast and high throughput Calcitonin II-Gen assay developed on the fully automated LIAISON instruments, which is suitable for high working capacity laboratories.

Design

Evaluation took place in Clalit HMO central lab, currently using the SIEMENS IMMULITE™ 2000 Calcitonin assay. Forty-one randomly outpatients’ serum samples collected from Clalit Central Laboratory, 42 from Clalit Haifa and Western Galilee Laboratory and nine from Clalit Jerusalem laboratory. The samples were tested on LIAISON XL and IMMULITE 2000 in parallel. Results were analysed according to patients’ gender and kit performance was tested.

Endocrine Abstracts (2013) Vol 32
Correlation between LIAISON® II-Gen and IMMULITE® 2000 calcitonin was analysed for: i) samples from Clalit Ahdim central laboratory, ii) Samples from Clalit Haifa and Western Galilee laboratory. iii) Samples from Clalit Jerusalem laboratory. Calculated total clinical agreement was 100, 95% and 89% respectively. Correlation and total clinical agreement were calculated on all three labs’ samples showed r=0.995, and 99% respectively. Correlation between LIAISON® and IMMULITE® Calcitonin of NEQAS samples showed r=0.9995. Precision of LIAISON® II-Gen was tested between and within runs and found to be 3.75–5.54% CV and 1.24–3.45% CV respectively. Functional sensitivity showed values of 1.136, 1.299 and 2.233 pg/ml. Dilution test showed linearity of r=0.9922.

Conclusions

High correlation observed between LIAISON and IMMULITE Calcitonin together with high clinical agreement. It is concluded that the LIAISON® II-Gen can be used as reliable and accurate kit for high throughput laboratories.

DOI: 10.1530/endoabs.32.P548

P549

Epidermal growth factor pathway as a possible target in the medical therapy of bronchial carcinoids

Teresa Gagliano1, Mariaenrica Bello1, Mariella Minoia1, Katiuscia Bentini1, Ettore degli Uberti1,2 & Maria Chiara Zatelli1,2

1Section of Endocrinology, University of Ferrara, Ferrara, Italy; 2Laboratorio in rete del Tecnopolo “Tecnologie delle terapie avanzate” (LTTA) of the University of Ferrara, Ferrara, Italy.

Bronchial carcinoids (BC) are rare tumors originating from endocrine cells dispersed in the respiratory epithelium. Currently, the main BC treatment is surgery, that can be curative in most of the cases, but is not feasible for large, infiltrating and metastatic disease. In these settings, medical treatment is often tried, being mainly represented by chemotherapy and radiation in the attempt to reduce tumor mass, while somatostatin analogues are employed for symptomatic control. Therefore it is important to identify new therapeutic targets and new molecules capable of providing adequate medical treatment for patients with BC for which surgical removal is not feasible. Growth factors which are important in experimental models of neuroendocrine tumors include epidermal growth factor (EGF), transforming growth factor (TGF) and TGFβ. EGF and TGFβ bind to the EGF receptor to stimulate the PI3K/RAS/RAF/MEK/ERK pathway, leading to the transcription of genes associated with cell proliferation, invasion and metastasis.

Our aim is to evaluate the effects of Sunitinib, a multi-targeted receptor tyrosine kinase (RTK) inhibitor, and NVP-BEZ235, a PI3K/mTOR inhibitor, on human primary BC cells cultures in order to verify the involvement of the EGF pathway in regulating crucial cellular processes.

Human BC primary cultures were treated with Sunitinib or NVP-BEZ235, alone or in combination with EGF. EGFβR expression, cell viability and caspase 3/7 activation were evaluated.

By immunofluorescences we found that EGFβR is expressed in all primary cultures. In addition, 100 nM NVP-BEZ235 and 10 μM Sunitinib inhibit cell viability by 30% and 20% (P<0.01), respectively. Both NVP-BEZ 235 and Sunitinib promote apoptosis (100%). 100 ng/ml EGF impairs the antiproliferative and pro-apoptotic effects of both Sunitinib and NVP-BEZ 235. These data suggest a possible role for EGFβR pathway as molecular target in the medical treatment of BC. Further studies are necessary to understand the molecular basis of this mechanism.

DOI: 10.1530/endoabs.32.P549

P550

Steroid-induced psychosis as a manifestation of ectopic ACTH secretion from metastatic poorly differentiated neuroendocrine tumour

Sviatlana Zhyzhneuskaya, Rasha Mukhtar, Simon Ashwell & Sath Nag

James Cook University Hospital, Middlesbrough, UK.

Case report

A 65-year-old fisherman presented with altered mental status, agitation, generalised oedema, dyspnoea, liver impairment and severe persistent hypokalaemia 2.2 mmol/l. History: COPD, IPF (on steroids since May 2012), enlarged paraaortic, subcarinal lymph nodes, bilateral adrenal hypertrophy. ACTH – 632 ng/l, total chromogranin A – 480 μl, 5-HIAA – 553 μmol/24 h. CT thorax/abdomen showed multiple liver metastasis. Pulmonary fibrosis, RUL nodule, enlarged paratracheal, subcarinal lymph nodes, bilateral adrenal hypertrophy. CT haed/MRI of pituitary were normal. Liver biopsy confirmed the presence of poorly differentiated (very high Ki67 index ~90%) small cell neuroendocrine tumour which positively stained for TTF1, CK7, CD56, AE1/3, chromogranin, synaptophysin. Positive staining for TTF1 and CK7 are sought to be in favour of primary lung lesion.

The diagnosis of poorly differentiated metastatic small cell neuroendocrine tumour with ectopic ACTH secretion was made. Patient was started on metyrapone 1 g 4 hourly. Ketonocazole 200 mg OD was added later. His cortisol and LFT had initially improved and potassium normalised. Oncology team put him on 3-month course of carboplatin with etoposide. Further investigations suggested for carcinoid in a form of octreotide scan were not recommended by Oncology Department due to its relative insensitivity in the settings of poorly differentiated neuroendocrine tumour. Patient passed away just in 4 months since presentation despite intensive chemotherapy.

Conclusion

We reported this case because of the interesting clinical presentation of an ectopic ACTH secretion exacerbated by exogenous steroid intake. This case also shows the importance of good differential diagnosis of hypokalaemia. Treatment options were limited due to the aggressive nature of the tumour.

DOI: 10.1530/endoabs.32.P550

P551

Adrenal incidentalomas – a retrospective analysis for the period 2001–2011

Monika Nývítová, Miroslav Vodák, Karolina Drbalová & Miroslav Zavoral

Military University Hospital Prague, Prague, Czech Republic.

Introduction

With the wider availability of imaging techniques there is an increasing number of newly diagnosed, accidentally found pathological formations in the adrenal glands known as adrenal incidentaloma (AI). Currently, the professional consensus is that hormonally active incidentalomas and those suspicious of malignancy should be indicated for surgery.

Methods

In our retrospective study, we analyzed data of 141 patients with a total of 160 AIs, who were followed up in 2001–2011 by the Outpatient Endocrinology Department of the Military University Hospital in Prague. Most AIs were up to 3 cm in size (77.5%), 11.25% had a size of 4–6 cm, and 11.25% were above 6 cm in size. Adrenalectomy was primarily indicated in all patients with AI greater than 6 cm. During the follow-up period, 12 AIs increased in size by 1 cm and four AIs by 2 cm or more. Hormonal activity was examined in all patients. Pathological hormonal overproduction was detected in 24 patients. During the 10-year follow-up period, a total of 36 patients underwent surgery, 21 because of the size of AI, nine for endocrine activity of the AI and three patients due to size progression of the AI. The result of postoperative histology was available for 21 incidentalomas. Malignant tumours accounted for 28.5%. All were larger than 6 cm and four were found to be hormonally active.

Results

All malignant tumours were larger than 6 cm. There is no doubt about the need to indicate adrenalectomy in these patients. Size progression of the AI had always been recorded already during the first 2 years of the follow-up. In patients with growth progression, detected hormonal activity or size 4–6 cm we use an individual approach and long-term follow-up.

DOI: 10.1530/endoabs.32.P551

P552

Androgen receptor expression in stromal and epithelial prostate cancer tissue specimens

Tamburriano Lara, Salvianti Francesca, Marchiani Sara, Nesi Gabriella, Lanciotti Michele, Carini Marco, Pinzani Pamela, Baldi Elisabetta & Forti Giovanni

University of Florence, Florence, Italy.

Prostate cancer (PCa) is one of the leading causes of tumor death in Western countries. Modifications in expression and functional alterations that involve the

Endocrine Abstracts (2013) Vol 32
androgen receptor (AR) have been implicated in the progression of PCs and in the development of androgen independence; however, the role of AR in these processes is still debated, as contrasting results have been reported in several studies evaluating the relation between AR expression and disease progression (Tamburrino et al., 2012). Such evaluations are performed in PC specimens where, however, tumor tissue may be mixed to stromal and normal. There is now evidence in the literature that AR role in PCs may vary depending on its location. Indeed, studies performed in animal models (Niu et al., 2008) pointed out the different role of epithelial (protective toward a malignant phenotype) vs stromal (leading to tumor aggressiveness) AR in PCs. The present study was undertaken to evaluate AR, EGFR, PSA and PTEN mRNA expression in stromal and epithelial compartments of PCs specimens following careful microdissection. So far we have analyzed 130 microdissected samples from 20 patients and further analyses are in progress. Preliminary results indicate that AR expression is correlated to that of EGFR in epithelial ($r=0.98$, $P<0.0001$) but not in stromal compartment. A similar correlation is found between AR and PSA in epithelial compartment ($r=0.67$, $P<0.002$). PTEN expression tends to decrease and to become undetectable in high-grade tumors as expected. AR expression appears to be lower in microdissected carcinoma areas with higher Gleson scores. In few patients with locally invasive tumors AR expression is higher in stromal respect to epithelial compartment. In conclusion, evaluation of AR expression in microdissected PCa specimens may reveal new insights on the role of the steroid receptor in PCa progression.

DOI: 10.1530/endoabs.32.P552

P553

Prolactinoma and vestibular schwannoma: a very rare association
Fariida Chentli, Faiza Belhimeur, Said Azzoug & Nora Soumeya Fedala
Department of Endocrine and Metabolic Diseases, Bab Oued Hospital, Algiers, Algeria.

Introduction
The occurrence of primary pituitary tumour and cerebral schwannoma in the same person is very rare. Only few cases have been reported so far. The mechanism of this association is still unclear.

Aim
Our aim is to report a man with two different brain tumours: a prolactinoma and a cerebellopontine schwannoma in order to discuss the possible mechanism of multiple neoplasms arising in the same person.

Case report
A man aged 50 years, without any history of neurofibromatosis, known to have a right ear malformation, consulted for a sensation of exorbitism of the right eye. Clinical and ophthalmological examinations were normal. But, cerebral MRI showed two tumours: one in the pituitary area and the second in the right cerebellopontine angle.

The first tumour is a prolactinoma: PRL = 1737 ng/ml ($n<15$), tumour size = 28×29×24 mm with a supra sellar extension and infra-sellar invasion filling the sphenoidal sinus. The second measures 18×16×22 mm with high signal intensity on T2 weighted MRIs, strongly enhanced after gadolinium injection suggestive of a schwannoma.

Conclusion
This association must be known as a new field of multiple neoplasms arising in the same person whose mechanism is still debated, especially in people without any personal history of radiation and neurofibromatosis.

Key Words
Vestibular schwannoma, pituitary tumour, prolactinoma.

DOI: 10.1530/endoabs.32.P553

P554

The adverse effects in sub-optimal mitotane doses: a retrospective study
Rene Baloeclus1, Rodica Petriță1,2, Dan Peretianu1, Anda Dumitrascu1,3, Roxana Miron1, Sorin Paun1,3, Mara Carsote1,2 & Catalina Poiană1,2
1Pathon Institute, Bucharest, Romania; 2Davila UMPs, Bucharest, Romania; 3SCM Poveinei, Bucharest, Romania; 4Constanta Hospital, Constanta, Romania; 5Floreasca Emergency Hospital, Bucharest, Romania.

Introduction
There are many side effects caused by mitotane and several are registered at drug levels lower than therapeutic doses.

Aim
We observed the mitotane side effects in patients treated for adrenal cancer.

Materials and methods
This is a retrospective study in adrenal tumors.

Results
Out of 56 patients included in a database with adrenal tumors, we found eight patients (14.25%) with adrenal cancer and histological confirmation of the disease. The mean age was 53.57 years. Twenty-five percent of patients were men. 62.5% of these patients were treated with mitotane and 25% of them with chemotheraphy. All patients with adrenal disease had unilateral adrenal tumors (50% of them were on the left side). Twenty-five percent of patients did not have metastasis at the moment of adrenal surgery. The mitotane was started after the adrenal surgery from 2 months to 2 years. All the patients had adrenal insufficiency immediately after surgery because of the previous Cushing disease caused by the tumor itself, so this was not registered later as a side effect to mitotane. The adverse reactions to mitotane were registered from very low doses were mild digestive effects as nausea were registered in all patients treated with mitotane from the first days. One female patient had multiforome erythema 10 days after starting the therapy. After temporary arrest of the mitotane, the drug was re-initiated and no erythema was found. Sixty-six percent of patients treated with mitotane had hypercholesterolemia at a level under 3.3 mg/dl. At least then 6 months from starting the therapy 33% of patients had peripheral neuropathy, anemia, and the men hypogonadism and painful gynecomastia. All these reactions were registered at very low doses of mitotane, far from therapeutical window of efficiency. No correlations of the side effects were found to the initial size of the tumor, to the severity of the clinical phenotype before adrenalectomy, or to the Weiss score.

Conclusion
The mitotane in adrenal cancer is a useful drug but numerous adverse reactions are registered from the beginning of the therapy, thus close follow-up is necessary.

DOI: 10.1530/endoabs.32.P554

P555

Type 1 gastric endocrine tumors as an autoimmune disease, with emphasis to lymphocytic thyroiditis
Ana Paula Santos, Joana Couto, Raquel Martins & Rui Silva
Instituto Português de Oncologia, Porto, Portugal.

Introduction
Type 1 gastric endocrine tumors (T1-GET) incidence is increasing world while mainly due to widespread use of upper endoscopy. Autoimmune disease (AID) is the hallmark of T1-GET, pernicious anemia is often found at presentation. Association with lymphocytic thyroiditis (LT) has been described.

Aims
Retrospective evaluation of GET data from patients (pts) followed at IPO-Porto, including the presence of other AID with emphasis to LT.

Patients and methods
Retrospective data from 48 GET patients files followed at Endocrine Tumors Clinic of IPO-Porto was reviewed. 20 pts were excluded because of insufficient data or diagnosis before 2006, because at that time classification was not performed. Age, gender, normal gastric mucosa (NGM), classification, stage, treatment, presence of pernicious anemia (PA), LT and other AID diseases; parietal (p-ab), intrinsic factor (IF-ab) and thyroid antibodies (TPO-ab, TG-ab), thyroid function (TF) and survival were evaluated.

Results
Age: 58.7 ± 10.2 years; F/M: 3/1; T1 = 85.7%, T2 = 0.0%, T3 = 14.3%. Median gastrin = 1107.6 ± 824.7 pg/ml. Two of four T3 were metastatic. T1-NGM showed atrophic gastritis (85.7%), intestinal metaplasia (61.5%) and HP positivity (15.8%). 85.7% (100% T1-GET) were submitted to endoscopic treatment. AID was identified in T1: PA 93.4%, vitiligo 1 pt, another has lupus erythematosus (LE) and Cronh’s disease (CD). Positive PC-ab 63.2% and FI-ab 5.6%. LT was identified in 33.3%. TPO and TG-ab were positive 22.4 and 11.1% respectively. Insufficient data concerning other DAI was found in 28.6–31.4%. 21.1% pts had either clinical or subclinical hypothyroidism. Thyroid nodules (TN) were diagnosed in 50% of pts who were submitted to US neck (n = 6). Three of four of T3 pts have died, 100% of T1 were alive.

Conclusion
As in other series, most of our GET pts are type1. In this group there was a high proportion of AID, including PA, vitiligo, LE and CD. One third of T1-GET had LT. Among these, one fifth had abnormal function tests and half of pts who were submitted to neck US had TN. All T1-GET must be evaluated in order to exclude association with other AIDs, especially LT. Prospective studies should be performed in order to increase our knowledge about this entity.

DOI: 10.1530/endoabs.32.P555
P556
Acromegaly, primary hyperparathyroidism and meningioma – an unusual association in an asymptomatic patient with MEN1 syndrome
Florabela Ferreira, Ema Nobre, Ana Wessling & Isabel Carmo
Santa Maria Hospital, Lisbon, Portugal.

Introduction
MEN1 is inherited as an autosomal dominant trait, with a prevalence of 2-20/100 000 in the general population. It is characterized by tumors involving the parathyroid glands, the endocrine pancreas and the pituitary. Other tumors are more rarely associated: adrenal adenomas, carcinoid tumors, pheochromocytomas, angiofibromas, lipomas, collagenomas and meningiomas. The presence of two or more of MEN1 associated tumors is diagnostic of the syndrome.

Case report
A 35-year-old man presented to the Endocrine consultation for investigation of asymptomatic multinodular goiter, with benign features in the neck sonogram. At physical examination the physician detected mildly enlarged hands and coarse facial features. The patient had been diagnosed with primary hypertension and kidney stones 2 years before. His medical history was otherwise irrelevant. Family history was negative for endocrine disease. The endocrine evaluation revealed mildly increased GH (3.3 ng/ml) and IGF-1 (704 ng/ml). The remaining anterior pituitary hormones and prolactin were normal. Throughout the oral glucose tolerance test, GH levels were equal or above 3.0 ng/ml, confirming the diagnosis of acromegaly. The cranial and sellar MRI revealed a left sellar mass 15×7 mm in diameter, inducing slight deviation of the pituitary stalk, indicating the presence of a pituitary adenoma. There was also a voluminous extra-axial left frontal tumor (43×37 mm) suggestive of a meningioma. Serum levels of calcium (11.3 mg/dl) and PTH (116.3 pg/ml) were increased, with normal renal function and 25OH vitamin D levels. Primary hyperparathyroidism (PHPT) was diagnosed. Insulinemia, gastrinemia and abdominal CT were normal. The results of the genetic test of the MEN1 gene are not yet available.

Conclusions
The phenotypic manifestations of acromegaly were the first clues to the diagnosis of MEN1 in this asymptomatic patient. The unusual association of acromegaly, PHPT and meningioma raised suspicion of a causative common genetic mutation and is diagnostic of MEN1 syndrome.

DOI: 10.1530/endoabs.32.P556

P557
Aggressive adreno-cortical carcinoma (ACC) associated with two rectal tumors (adenocarcinoma and neuro-endocrine) and somatic Kras mutation without microsatellite instability: is there a link?
Clara Leroy1, Christine DeCao1, Wassila Karrouz1, Anne-Claire Le Guillou1, Alexandra Deraveux1, Marie-Pére Buissine1, R Pébay1, Emmanuelle Letetre1, Robert Canazzo1,2, Francois Pattou1,2 & Marie-Christine Vantyghen1,3
1Endocrinology Department – CHRU, Lille, France; 2Oncogenetic Department – CHRU, Lille, France; 3Anatomopathology Department – CHRU, Lille, France.

Introduction
Aggressive adreno-cortical carcinoma (ACC) is a rare, aggressive malignancy, with poorly understood molecular pathogenesis. As a result, therapeutic options are currently limited, surgery being currently the lone curative modality. Most cases of ACC are sporadic, although some familial cancer syndromes (Li–Fraumeni, Beckwith–Wiedemann, MEN1, Carney complex, congenital adrenal hyperplasia, etc.) are associated with an increased incidence of ACC. The genes involved in these syndromes, the adrenocorticotropic hormone-cAMP-protein-kinase-A and the β-catenin gene (CTNNB1), which lead to constitutive activation of Wnt signaling, are also implicated in ACC tumorigenesis. Understanding these pathways lead to targeted therapy such as IGF, mTOR, steroidalogenic factor-1, and MDR1 antagonists. Besides, rare cases of ACC are associated with colon cancer, sometimes associated with APC gene mutation and Lynch syndromes. We report a new case.

A partially deaf 43-year-old woman, with a narrow face, was diagnosed with ACC in reason of a painful 12 cm heterogeneous adrenal mass, secreting cortisol and androgens with angi-invasion impeding surgical resection. PET-PDG showed adrenal, lumbar and rectal uptake. Rectal biopsies showed a well-differentiated adenocarcinoma and a moderately-differentiated neuro-endocrine tumour. Rapidly occurring liver metastases were in favour of poorly-differentiated ACC. The patient’s father had died from colonic perforation and her son had ulcerative colitis. Kras gene analysis on the colorectal carcinoma showed a somatic mutation (exon 2, V12G), but no microsatellite instability (phenotype MSS), rebutting Lynch syndrome. Kras and TP53 analysis in blood and liver metastasis are under investigation.

In conclusion, i) the association of two colorectal cancers with aggressive ACC is a particular challenge to define the priority of treatment between these two tumours; ii) the somatic Kras mutation inducing activation of the Ras/Raf/MEK/ERK pathway occurs in 40% of colorectal cancer but its role in ACC remains unknown. The involvement of Kras mutations in ACC could lead to new therapies such as Kras or PIK3 kinase inhibitors.

DOI: 10.1530/endoabs.32.P557

P558
Patient-specific management of paragangliomas
H M Christine Leong & John Miell
Lewisham Hospital NHS Trust, London, UK.

Introduction
Paragangliomas (PGLs) are extra-adenal, neural crest-derived neuroendocrine tumours. There are sympathetic (usually abdominal and thoracic regions) or parasympathetic PGLs (head and neck). Catecholamine excess usually occurs in sympathetic PGLs.

Case
A 34-year-old lady initially presented with left-sided neck swelling. She was diagnosed with left cervical PGL which was excised. Twenty years later, she noticed another lump in the same region and functional imaging indicated a second primary disease and underwent repeat surgery. Subsequent genetic testing revealed the succinate dehydrogenase enzyme D (SDHD) mutation. Her sister was also diagnosed with cervical PGL. Two years after surgery, she described daily intermittent forceful palpitations and was hypertensive with BP 170/95. Urinary catecholamine collections, plasma normetanephrine and metanephrine levels were normal. She had anatomical CT and MRI imaging, octreotide scan and MIBG scintigraphy. Functional imaging revealed multiple sites in her mediastinum and her case was discussed at the regional neuroendocrine tumour meeting. As she was intolerant of phenoxybenzamine, doxorubicin was started followed by propranolol. She had surgical removal of the right cervical, subclavian and aortic root PGLs. Recently, she was admitted with central chest pain associated with elevated cardiac enzymes. ECG demonstrated lateral ST depression, and an echocardiogram showed mid to apical, segmental and lateral wall hypokinesis with apex ballooning. Coronary angiography revealed normal arteries. Repeat echocardiogram showed ventricular function had returned to normal. A diagnosis of Takotsubo cardiomyopathy was made. Urinary catecholamine, plasma normetanephrine and metanephrine levels were normal throughout.

Conclusions
Head and neck PGLs are usually non-functioning and present as space-occupying symptoms. It is unusual she had symptoms of catecholamine excess. Functional imaging proves invaluable and this highlights the need to discuss complex cases in multidisciplinary meetings. With reported associations between Takotsubo cardiomyopathy and catecholamine-producing PGLs and phaeochromocytomas, could this episode be a manifestation of her PGL? There should be a low threshold for functional imaging for PGLs in patients with familial genetic mutations.

DOI: 10.1530/endoabs.32.P558

P559
Malnutrition cause of Secondary Osteoporosis after surgical operation of Glucagonoma
Biljana Jovanoska, Irfan Ahmeti, Snezana Markovik Temelkova, Gordana Pemovska, Cedomir Dimitrovski & Iskra Bitovska
Clinic of Endocrinology, Skopje, Macedonia.

Introduction
Glucagonoma is a rare condition with annual incidence 1 in 20 million, associated with diabetes mellitus, dermatitis, deep vein trombosis and depression.

Case report
A 55-year-old woman patient was hospitalized at our department because of intense discomfort of the skin lesions that were pruritic and painful, erythematous area of skin with blisters that break after a few days, red tongue, cracks on the mouth corners. She had a constant weight loss accompanied with bloody diarrhea.
Her weight was 36 kg, height 150 cm and her BMI was 16. We made 75 g OGTT and it was normal. She was misdiagnosed like contact dermatitis magnus et pedum, stomatitis protetica, erythema exsudativum multiforme, colitis. On the examination she had chelitis angularis, atrophic glossitis, stomatitis, normochromic normocytic anemia and the Hct was 0.27, se 70/100. She had dermatological changes – erythematous patch, blisters centrally, erosions, crusts, heals with hyperpigmentation. We made a lab test and we got that her glucagonemia was increased twice than normal. The normal values are 200 ng/l and she had 400 ng/l. We made a CT scan where a round form of a tumor was noticed in the pancreas with dimensions 5 cm width and 8 cm length. After that, she underwent a surgical operation and the surgeon made a distal spleenopancreatectomy to remove the tumor. The tumor immunohistochemistry was positive of glucagon, synaptophysin and chromogranin-A. After the operation, she suffered from malnutrition and she came again at our department to check herself for osteoporosis. We made a DXA scan and we saw that she had a generalized secondary osteoporosis caused due to malnutrition after operation (T score = -4.0 on the spine, T score = -3.8 on the right hip and T score = -3.6 on the left hip).

Conclusion

Long-term misdiagnosed glucagonoma explain appearance of other co-morbidities such as osteoporosis and anemia.

DOI: 10.1530/endoabs.32.P559

---

**P560**

Clinical, biochemical, genetic and histological features of composite pheochromocytoma/ganglioneuroma adrenal tumors: a series of seven cases from two French academic centres

Alice Bertron1, Françoise Gobet2, Estelle Louiset2, Milene Tetsi-Nomigni2, Luca Gramolato2, Emmanuelle Leteutre1, Philippe Grise2, Laurent Yon3, Jean-Louis Werneaux4 & Hervé Lefèbvre1,3

1Department of Endocrinology, University Hospital of Rouen, Rouen, France; 2Department of Pathology, University Hospital of Rouen, Rouen, France; 3INSERM U982, Normandy University, IBIS, Mont Saint Aignan, France; 4Department of Pathology, University Hospital of Lille, Lille, France; 5Department of Urology, University Hospital of Rouen, Rouen, France; 6Department of Endocrinology, University Hospital of Lille, Lille, France.

Introduction

Adrenal pheochromocytomas have the same embryonic origin, i.e. the neural crest, as peripheral neuroblastic tumors such as ganglioneuromas, ganglioneuroblastomas and neuroblastomas. Ganglioneuromas are benign and silent tumors in that they usually do not secrete catecholamines in contrast to pheochromocytomas. Rarely, they can associate with pheochromocytomas to form composite tumors.

Patients and methods

We have retrospectively studied seven patients with pheochromocytoma/ganglioneuroma composite adrenal tumor followed up in two French academic departments of endocrinology. The clinical, biochemical, genetic and histological characteristics of the tumors were collected. In addition, immunohistochemical labelling of tumor slices with specific antibodies directed against the key enzyme for adrenaline synthesis phenylethanolamine N-methyltransferase (PNMT) were carried out in order to better individualize the two components of the neoplasms.

Results

In all cases, association of the adrenal mass with clinical and biological signs of catecholamine excess led to the initial diagnosis of pheochromocytoma followed by adrenal surgery. The ganglioneuroma components of the neoplasms were identified at pathological examination of the tissues. Four patients carried germinal mutations affecting the NF1 gene, whereas three harbored MYC-associated factor (MAX; one patient) genes. Five patients harbored associated neoplasias and two patients had subclinical hypercortisolism related to hyperplasia of the adrenal cortex adjacent to the tumors. Immunohistochemical labelling of tumor sections allowed perfect discrimination of the two tumor tissue components by revealing intense staining of pheochromocytes contrasting with no signal in ganglion cells.

Conclusion

We report a large series of adult adrenal pheochromocytoma/ganglioneuroma composite tumors. In addition, we show that, in addition to routine histological examination of the tumor tissues, immunohistochemical studies with antibodies to PNMT can be helpful for the diagnosis of the disease by facilitating identification of the two tumor components.

DOI: 10.1530/endoabs.32.P560

---

**P561**

Everolimus treatment in a series of patients with advanced neuroendocrine tumors

Donato Iacovozzo1, Francesca Lugli1, Francesca Plastino1, Giovannina Schiavinato2, Alessandra Cappola3, Guido Rindi3, Alfredo Pontecorvi1, Laura De Marinis1 & Carlo Antonio Mario Barone1

1Endocrinology – Catholic University Policlinico A. Gemelli, Rome, Italy; 2Medical Oncology – Catholic University Policlinico A. Gemelli, Rome, Italy; 3Pathology – Catholic University Policlinico A. Gemelli, Rome, Italy.

Introduction

Everolimus is an oral mTOR inhibitor that exerts antineoplastic effects inhibiting cell proliferation, survival and angiogenesis. Its activity in advanced neuroendocrine tumors (NETs) has been demonstrated in controlled trials and everolimus was approved by the FDA for the treatment of progressive, advanced NETs in May 2011.

Materials and methods

We treated with everolimus, at the dosage of 10 mg once daily, 14 patients with advanced, progressive, low- or intermediate-grade NETs for a mean period of 11 months. Somatostatin analogues treatment was continued in all patients. Twelve of 14 patients had previously undergone peptide receptor radionuclide therapy (PRRT) with either Lutetium or Yttrium.

Results

According to RECIST criteria, stable disease was observed in 9/14 patients and partial response was achieved in 2/14 patients. Median progression-free survival was 12.0 months. Drug-related adverse events included stomatitis (7/14), hyperglycaemia (7/14), hypertriglyceridaemia (5/14), pneumonitis (4/14), hematologic toxicity (4/14), peripheral oedema (4/14) and rash (2/14). Grade 3 and 4 adverse events included pneumonitis (three cases) and thrombocytopenia (two cases). Dose reduction was required in 5/14 patients.

Conclusion

Our data confirm the efficacy of everolimus in the treatment of progressive, advanced NETs. The apparently higher rate of grade 3 and 4 adverse events is probably related to the high proportion of patients in our series that had previously undergone PRRT, as it may enhance everolimus potential myelotoxicity.

DOI: 10.1530/endoabs.32.P561

---

**P562**

Are hibernoma or lipoma a marker of type 1 multiple endocrine neoplasia (MEN1) aggressiveness?

M Kamoun1, W Karrouz1, K Le Mapihan1, M D’Herbomez2, A Beron2, R Ciazzo1, N Porchet1, F Pattou1, J L Wémeau1 & M C Vautrym1

1Service d’Endocrinologie et maladies Métaboliques, Hôpital Claude Huriez, CHRU de Lille, lille, France; 2Service de médecine nucléaire, hôpital Huriez, CHRU de Lille, lille, France; 3Service de Chirurgie générale et endocrinienne, CHRU de Lille, lille, France; 4Pôle de Biologie-Pathologie-Génétique, CHRU de Lille, lille, France.

MEN1, autosomal dominant, is characterized by combined tumours of the parathyroid glands, pancreatic islet cells, and the anterior pituitary, sometimes associated with other endocrine (adrenocortical, foregut carcinoid) and noneocrine (lipoma, angiofibroma, collagenoma, ependymoma, meningioma) neoplasia. It is caused by inactivating mutations of the MEN1 tumour suppressor gene (chromosome 11q13), encoding menin. Menin, involved in activation of gene transcription, regulates PPARα-dependent adipocyte differentiation (Dreijerink Mol Cell Biol 2009), whereas PPARα is expressed in several MEN1-associated tumour types.

We report two cases of unrelated obese male patients presenting with aggressive MEN1 and large either hibernoma or lipoma. Case 1, 39-year-old, without any family history, was diagnosed with Zollinger–Ellison syndrome with high gastrin, pancreatic polypeptide and glucagon level, invasive macroprolactinaemia, high gastrin, pancreatic polypeptide and glucagon level, invasive macroprolactinaemia, hyperparathyroidism, large either hibernoma or lipoma. Case 2, 25-year-old, belonging to a MEN1 family (c.1546dupC/p.Arg516Pro/SX15), was diagnosed with severe hyperparathyroidism (with ectopic parathyroid gland), five pancreatic endocrine tumors (with hyperplagcagonemia) and a 13 cm FDG-negative lipoma of the left iliac muscle.

DOI: 10.1530/endoabs.32.P562

---

Endocrine Abstracts (2013) Vol 32

15th European Congress of Endocrinology 2013
In conclusion, hibernomas are benign tumors with morphological features resembling brown fat. Their PET-FDG uptake raises differential diagnosis issues with liposarcomas and metastasis. As lipomas (Vortmeyer J Natl Cancer Inst 1998), they consistently display cytogenetic rearrangements, involving chromosome band 11q13 (Gisselsson Am J Pathol 1999). MEN1 display a low expression in hibernomas whereas the expression of genes up-regulated in brown fat (PPARγ, UCP1) is high (Nord PNAS 2011). These associations raise the question of the relationship between adipose tissue and cancer genesis or MEN1 aggressiveness.

DO: 10.1530/endoabs.32.P562

**P563**

Malignant pheochromocytoma: vertebral metastasis 18 years after surgery. The importance of prolonged follow-up

Joana Saraiwa, Isabel Paiva, Leonor Gomes, Maria Silveira, Carolina Moreno, Daniela Guellho, Gonçalo Costa, Maria Mosteiro, Gracinda Costa, José Casanova, Manuela Carvalheiro & Francisco Carrilho Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal.

**Introduction**

Malignant pheochromocytomas are rare. Metastatic disease may be present at the time of diagnosis or may only be evident after. Prognosis is poor. Currently there is no effective cure.

**Case report**

We describe the case of a 66-year-old woman with a history of pheochromocytoma submitted to left adrenalectomy in 1992. In the past 10 years, she complained of episodes of dorsal back pain associated with hypertensive peaks and tachycardia. In 4/2010, a dorsal MRI was performed revealing D10 pathologic fracture with moderate spinal compression, compatible with bone metastasis. MIBG-SPECT/CT: increased uptake in D10. Guided biopsy: the lesion was metastasis diagnosed after 18 years

**Conclusion**

Twenty-seven (58.7%) were men. The mean age at diagnosis was 44.5 (15.5) years. 82.6% were sporadic, multiple endocrine neoplasia type 1 was diagnosed in 15.2% and neurofibromatosis type 1 in 2.2%. Localization was 48.9% pancreatic, 40% gastrointestinal tract, 6.7% bronchial and 4.4% thymic. Incidental diagnosis occurred in 11.4% of the cases. 62.9% presented hormone hypersecretion symptoms. In those with clinical symptoms, the mean time until diagnosis was of 7.4 (12.5) months with a median of 3 months. At diagnosis 69% of the cases presented distant metastases. The most common site of metastases was liver (100%). The most commonly carried out imaging studies for the primary tumor and metastases was computed tomography (CT) scan 89.1 and 100% respectively. Overall, about 97.7% of the patients underwent surgery most of them with curative intent. 33.8% underwent hepatic transplant. 55.5% were treated with somatostatin analogues, 19.4% with chemotherapy, 7.5% with lutetium and 2.5% with irinotecan.

After a mean follow-up of 7.2 (5.0) years for pancreatic NET and 8.8 (5.3) years for the intestinal NET, the survival was 81 and 66.5% respectively.

**Conclusions**

The NETs of pancreatic location are the most common in our series. Metastatic disease is frequent during follow-up and in most NETs is already present at diagnosis. Surgery is the first-line treatment for the NETs regardless of their location. Up to one third of the patients received a hepatic transplant, being this method a real option for those patients with metastases confined to the liver.

**DO:** 10.1530/endoabs.32.P564

**P564**

Gastroenteropancreatic neuroendocrine tumors: descriptive study in a reference Spanish hospital

Beatriz León de Zayas, María Isabel del Olmo García, Agustín Ramos Prol, Antonia Pérez Lázaro, Susana Tenes Rodrigo, Roser Querol Ripoll, Matilde Rubio Almanza, Rosa Cámara Gómez & Juan Francisco Merino Torres La Fe University Hospital, Valencia, Spain.

**Objective**

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are relatively infrequent. We present a descriptive study of GEP-NETs of a reference Spanish hospital.

Patients and methods

Forty-six patients were diagnosed of GEP-NETs during the period 1993–2011. Data regarding demographic, clinical, analytical, anatomicopathological and diagnostic variables were collected. Results are expressed as mean ± SD.

**Results**

Analysis of the type of tumor, 5% were gastrinomas, 7.5% with lutetium and 2.5% with irinotecan. A 76-year-old female was admitted with suspected hypercortisolism for further diagnostic tests. Increased serum cortisol levels with loss of circadian rhythm (1290, 1083, 1264, and 942 nmol/l at 0800, 1600, 2000, and 2400 h respectively) increased basal urinary free cortisol (basal 2804–2606 nmol/d), non-suppressible in 2 mg (1050 nmol/d) respectively 8 mg dxm test (2555 nmol/d), with increased ACTH levels (282–251 pg/ml) confirmed ACTH-dependent Cushing syndrome (CS). MRI of the pituitary was normal, CT of thorax and abdomen showed only hyperplastic adrenal glands. Bronchoscopic biopsy was negative, PET/CT with 18FDG showed pathologic lesion in inferior mediastinum. Patient refused to undergo thoracic surgery, thus KTZ at a dose of 400 mg/d was started. Patient tolerated medical treatment without any side effects, UFC levels decreased to normal levels (86 nmol/d) and good effect of KTZ persisted even after reduction of the dose to 100 mg/d (UFC 43.58 nmol/d). At the present time, patient is on this dose of KTZ 36 months with normalized cortisol status.

**Discussion**

A 76-year-old female was admitted with suspected hypercortisolism for further diagnostic tests. Increased serum cortisol levels with loss of circadian rhythm (1290, 1083, 1264, and 942 nmol/l at 0800, 1600, 2000, and 2400 h respectively) increased basal urinary free cortisol (basal 2804–2606 nmol/d), non-suppressible in 2 mg (1050 nmol/d) respectively 8 mg dxm test (2555 nmol/d), with increased ACTH levels (282–251 pg/ml) confirmed ACTH-dependent Cushing syndrome (CS). MRI of the pituitary was normal, CT of thorax and abdomen showed only hyperplastic adrenal glands. Bronchoscopic biopsy was negative, PET/CT with 18FDG showed pathologic lesion in inferior mediastinum. Patient refused to undergo thoracic surgery, thus KTZ at a dose of 400 mg/d was started. Patient tolerated medical treatment without any side effects, UFC levels decreased to normal levels (86 nmol/d) and good effect of KTZ persisted even after reduction of the dose to 100 mg/d (UFC 43.58 nmol/d). At the present time, patient is on this dose of KTZ 36 months with normalized cortisol status.

**DO:** 10.1530/endoabs.32.P565
P567
Therapeutic difficulties in elderly patients with insulinoma
Elżbieta Andrysiak-Mamers1, Teresa Starzynska1, Ewa Zochowska1, Andrzej Białek2, Elżbieta Sowińska-Przepińska1 & Anhelli Syrenca2
1Department of Endocrinology, Metabolic Diseases and Internal Diseases, Pomeranian Medical University, Szczecin, Poland; 2Department of Gastroenterology, Pomeranian Medical University, Szczecin, Poland.

Introduction
It is believed that hypoglycemia in the elderly is a dangerous condition and may result in stroke and death. We observed five female patients with insulinoma and over 20-year-long survival.

Material
The material includes five female with the diagnosis of insulinoma. Patients' age ranged from 78 to 93 years while disease duration ranged from 21 to 34 years.

Methods
In all the patients, the diagnosis of insulinoma was based on glucose, insulin and C-peptide levels in the fasting test, while the presence of focal lesion in the pancreas was confirmed in CT, MRI and EUS.

Results
At the time of diagnosis, mean fasting glucose level was 31.4 mg/dl (+9.6), insulin – 19.5 μU/ml (+14.2) and c-peptide – 8.2 ng/ml (+4.9). In three patients, disease progression was observed after many years of diazoxide therapy. These women have not been qualified for surgery because of their general status. Alcohol ablation of insulinoma was attempted in three patients, but the relief of clinical symptoms after EUS-guided administration of 5 m of ethanol was obtained in only one patient. In the remaining two women, the procedure could not be performed for technical reasons. These patients had receptor scintigraphy with octreotide and blood glucose levels were evaluated in the test with 100 mg octreotide – significant increase in glucose levels was observed in hours 5, 6 and further on, persisting up to 12 h (mean baseline glucose level 41.7 mg/dl; glucose levels following octreotide administration in subsequent hours – 163, 195, 221 mg/dl). In both patients, long-acting somatostatin analogues were started with good clinical effect.

Conclusion
Ethanol ablation of insulinoma and treatment with somatostatin analogues is an alternative in patients who are not good candidates for surgery and in whom diazoxide therapy is ineffective.

DOI: 10.1530/endoabs.32.P567

P566
An analysis of genotype–phenotype correlations and variable clinical expression in families with multiple endocrine neoplasia type 1
Agata Jabrocka-Hybel, Anna Skalniak, Jakub Piatkowski, Dorota Pach & Alicja Hubalewska-Dylewicz
Department of Endocrinology Jagiellonian University, Krakow, Poland.

Multiple endocrine neoplasia type 1 is an inherited syndrome that is caused by a germline mutation in the MEN1 gene encoding a tumour-suppressor protein, menin. Currently, no clear genotype–phenotype correlation has been established between clinical forms and MEN1 gene mutations. The aim of the study was clinical characteristics in relation to MEN1 gene mutation in families with MEN1 syndrome treated in our department. To date, genetic testing including complete sequencing of the coding region (exons 2–10) showed significant changes in four families with MEN1 syndrome. In each family, different type of mutation was found and only one of them was previously described. Clinical characteristics and aggressiveness of the disorder were different in each family. Our mutations were localized in the following exons: 4 (c.790_795dupCTGCAG), 7 (c.945delG), 9 (c.1246_1248delGCC), 10 (c.1393C>T). Loss of heterozygosity in tumour tissue will be studied by microsatellite analysis in the family with mutation in exon 9 to confirm its significance.

DOI: 10.1530/endoabs.32.P566

P568
Therapy with 177Lu marked somatostatin analogues in a case of pancreatic metastatic neuroendocrine tumor
Sandra Belo1,2, Ines Lucena2, Ana Paula Santos3, Luis Pedro Afonso4, Cristina Sanches3 & Hugo Duarte2
1Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar de São João, Porto, Portugal; 2Department of Nuclear Medicine, Instituto Portugues de Oncologia, Porto, Portugal; 3Department of Endocrinology, Instituto Português de Oncologia, Porto, Portugal; 4Department of Pathology, Instituto Português de Oncologia, Porto, Portugal.

Introduction
Conventional systemic therapies have limited role in metastasized neuroendocrine tumors (NET). Therefore an increasing role is attributed to 177Lu labeled somatostatin analogues (SA).

Case
Man, 52 years, referred because of NET, diagnosed following liver biopsy for hepatic nodules (liver tissue infiltrated by NET, compatible with metastases). Endoscopic ultrasound revealed pancreatic nodular formation, 40 × 24 mm; 9mTc scintigraphy revealed foci of hyperfixation in the liver, midline abdominal projection and left kidney upper pole. Serotonin levels were 183.0 ng/ml (40–450), ASH 3.7 mg/24 h (2.0–10), chromogranin A (CgA) 286 ng/ml (<134), gastrin 118 ng/ml (<108), insulin 6.4 μU/ml (6–30) and glucagon 472 pg/ml (100–190). Patient underwent body-caudal pancreatectomy. Histology revealed well differentiated pancreatic NET. G2, 2–10 mitoses/IFIA, Ki67 3–20%, peripancreatic soft tissue, lymphovascular and perineural invasion, lymph nodes metastasis, positivity for Cam52, CgA, synaptophysin and NES. 177Ga-DOTANOC-PET revealed liver, lumbarto, periceliac lymph nodes foci of hyperfixation. Embolization of liver metastases and SA treatment was started. Second 177Ga-DOTANOC-PET revealed new hepatic foci. Because of disease progression therapy with 177Lu-DOTATATE was performed. 177Ga-DOTANOC-PET after three cycles of 177Lu revealed fewer liver foci and no evidence of adenopathy.

Conclusion
Treatment with radionuclabelled SA is a promising strategy in patients with inoperable or metastatic NET.

DOI: 10.1530/endoabs.32.P568

P569
A case of pheochromocytoma that recognized as panic disorder before its exact diagnosis
Yohei Muroya1, Naoko Kugama2, Masanori Shimoaida2, Kaoru Tsuchawa2, Erisa Sorimachi2, Hiroko Arikoma1 & Kazufumi Honda1
1St. Luke’s International Hospital, Chuo-ku, Tokyo, Japan; 2Tokyo Metropolitan Hrioo Hospital, Shibuya-ku, Tokyo, Japan.

A 44-year-old female patient visited our department for the treatment of diabetes. Her diabetes was pointed out 1 year before and was resistant to the treatment with oral hypoglycemic agents. From around the same time, she complained of repeated attacks consist of headache, palpitation, sweating and nausea. She had suffered from obsessive compulsive disorder for 20 years and her psychiatrist recognized that these attacks were caused by some psychological problems such as panic disorder. However, neither anti-depressant nor anxiolytic agent was effective to improve her recurrent symptoms. Because her diabetes was resistant to the treatment, abdominal ultrasonography was done. It showed large left adrenal mass (approximately 10 cm in diameter). Plasma levels of cortisol and aldosterone were normal. However, 24 h urine excretions of epinephrine, norepinephrine and total metanephrines were markedly increased (epinephrine 171 μg/d, norepinephrine 934 μg/d and total metanephrines 29.9 μg/d). Scintigraphy with 131I-metaiodobenzylguanidine (MIBG) revealed high levels of accumulation at left adrenal mass. From these results, left adrenal mass was diagnosed as pheochromocytoma. The left adrenal mass was removed surgically and the pathological findings revealed typical characteristics of pheochromocytoma. Both blood pressure and blood glucose levels were normalized after surgery. Furthermore, her recurrent panic attack-like symptoms disappeared. In conclusion, this case shows us the importance of excluding physical abnormalities before making a diagnosis of panic attack-like symptoms.

DOI: 10.1530/endoabs.32.P569
Various neuroendocrine tumors in a multiple endocrine neoplasia type I family with the same genetic background
Kristiitn Sepp1,2, Ewa Cisjak1,2, Sandor Magony1,3, Janos Julesz1,3, Attilla Patocs2,3, Karoly Racz2 & Zsuzsanna Valkusz3
1First Department of Medicine, University of Szeged, Szeged, Hungary; 2Second Department of Medicine, Semmelweis University Budapest, Budapest, Hungary.

Introduction
Multiple endocrine neoplasia (MEN) type 1 is a rare congenital disease with genetic background. The MEN-1 gene encodes menin protein, that acts as a tumor suppressor. Mutation of one allele and the inactivation of the other allele of this gene lead to clonal proliferation and to the development of tumors. The clinical manifestation of MEN type 1 is a combination of endocrine (parathyroid adenomas, entero-pancreatic neuroendocrine tumors, pituitary tumors) and non-endocrine tumors.

Case report
A 38-year old male patient’s investigation was initiated by diffuse disturbances of bone metabolism. Diagnostic procedures revealed presence of primary hyperparathyroidism due to a parathyroid adenoma associated with a pituitary adenoma, a malignant pancreatic neuroendocrine tumor, neuroendocrine cancer of the thymus, hormonally inactive bilateral adrenocortical adenomas and a non-endocrine tumor (facial angiobroma). The co-existence of all these components witnessed for the diagnosis of MEN type 1. The parathyroidic, pancreatic neuroendocrine and the thymic tumors were surgically removed. For his hyperpocalcinemia and the pancreatic and thymic tumors, he has been kept under continuous bromocriptine and somatostatin analogue therapies, simultaneously. The MEN-1 mutation screening proved a new stop codon mutation CAGTTAG leading to early stop of protein synthesis. One of the two daughters of the patient was also positive for the same mutation, however, she has not presented any clinical symptoms so far. Their genetically positive older brother (18 years) suffered from hypoglycaemias due to pancreas neuroendocrine tumor. In addition he has hypoparathyroidism that has not yet been operated.

Conclusion
In the present family history, the index patient showed all the major components of MEN type 1. With the aid of genetic screening, the clinical diagnosis was confirmed and the affected family members have been identified. Early diagnostics, continuous observation and initiation of proper therapeutic approaches for their presumed MEN-1 associated tumors became possible.

DOI: 10.1530/endoabs.32.P570

P571
Visceral and tumour abnormalities in subjects with acromegaly
Meriem Haddad, Katia Daffeuer, Lina Akkaiche, Nadia Kalalate & Farida Chentli
Department of Endocrine and Metabolic Diseases, Bab Oued Hospital, Algiers, Algeria.

Introduction
Acromegaly is a relatively rare disease with numerous complications. Our aim is to look for visceral abnormalities and tumour development in subjects with GH and insulin like GH (or IGF) excess.

Subjects and methods
It is a retro-and prospective study that takes in account 112 patients at diagnosis, with pituitary tumours secreting GH, or mixed tumours secreting prolactin and GH diagnosed between 1980 and 2012. They all were questioned and examined. They also had heart (clinical, ECG and echosonography), pulmonary (clinical ± polysomnography), gastro intestinal (coloscopy, abdomen ultrasound (US)), thyroid (US ± scintigraphy), prostatic (US, total and free prostatic acid phosphates: n=16), and bone (standard radiographs, bone mineral density) explorations.

Results
High blood pressure was observed in 31.53%, cardiomyopathy in 33.65% and sleep apnea (SA)=15%. Severe bone abnormalities were seen in 12.12%. For organomegaly, we observed 75% benign prostatic hypertrophy, 40% goiters, 13% splenomegalies and 7.89% hepatomegalies. Concerning neof ormations, we observed 7.89% colon polyps and 2 (1.7%) thyroid cancers.

Conclusion
In this group, cardiovascular complications, prostatic hypertrophies, and organomegalias are as frequent as in literature reports. For SA our results are certainly under estimated. For colonic polyps and malignant tumors our results should be low compared to some authors’ results.

DOI: 10.1530/endoabs.32.P571

P572
The clinical significance of tumor suppressor gene methylation, expression in nodular thyroid disease
Feng Wei, Zhaoxia Wang & Yun Wu
Department of Endocrinology, The First Affiliated Hospital of Baotou Medical College, Inner Mongolia University of Science and Technology, Baotou, China.

Objective
The tumor suppressor gene methylation lead to gene silencing, it plays an important role in thyroid tumor occurrence and development. This study examined the tumor suppressor gene (PTEN, RASSF1A, DAPK, RARβ) DNA methylation and mRNA expression status in the peripheral blood of patients with nodular thyroid disease. Discuss its clinical significance. For the benign and malignant thyroid nodules early identification of molecular diagnosis is based.

Method
Select in September 2007–December 2011 a total of 200 cases of nodular thyroid disease diagnosed (including 66 cases of patients with nodular goiter, 50 cases of thyroid adenoma, 24 cases of thyroid cancer and 60 cases of normal control group as a research object, mining fasting venous blood, by the specificity MSP-PCR methods to detect PTEN, RASSF1A, DAPK and RARβ methylation, by RT-PCR method to detect the peripheral blood of the four genes mRNA expression using SPSS 13.0 statistical software.

Result
In the high methylation status of DAPK, RARβ, PTEN, RASSF1A gene in the peripheral blood of thyroid cancer, adenoma and nodular goitre patients, and to compare the methylation rate of thyroid cancer > adenoma > nodular goiter. Tip the four genes promoter methylation is common in molecular biological events in the peripheral blood of thyroid tumors. Closely related to the occurrence and development of thyroid tumors. The four genes mRNA expression in the peripheral blood of thyroid cancer and adenoma reduce or even missing, and was negatively correlated with four gene methylation. Tip four genes promoter methylation may be one of the reasons causing gene expression to reduce the missing. The four genes promoter methylation and mRNA expression is realated with lymph node metastasis in thyroid cancer patients. No relationship between nodule size, calcification and ECT.

Conclusion
MSP and RT-PCR method combined detection of nodular thyroid disease in peripheral blood of tumor suppressor gene RARβ, of DAPK and PTEN, RASSF1A gene methylation and expression. For early malignant and benign thyroid nodules to identify the diagnosis. Determination of MSPDNA and RNA in peripheral blood play an important role in tumor early diagnosis, cancer screening and other aspects.

DOI: 10.1530/endoabs.32.P572

Endocrine Abstracts (2013) Vol 32
before any surgery, plasma calcitonin twice a year and if it is rised PET-CT for
detection of metastasis for modular thyroid carcinoma.
DOI: 10.1530/endoabs.32.P575

Female reproduction

P574
Subcutaneous adipose tissue distribution and metabolic parameters in
lean women with polycystic ovary syndrome
Lina Zabuliene1,2 & Jurgita Urboniene3
1Clinics of Rheumatology, Traumatology-Orthopedics and Reconstructive
Surgery, Faculty of Medicine, Vilnius University, Vilnius, Lithuania;
2Antakalnis out-patient clinic, Vilnius, Lithuania; 3Infectious Diseases and
Tuberculosis Hospital, Vilnius University hospital “Santarsikiu klinikos”,
Vilnius, Lithuania.

Background
The objective of the study was to compare distributions of subcutaneous adipose
 tissue and metabolic parameters in lean women with PCOS and lean healthy
women.

Materials and methods
PCOS women (according to Rotterdam criteria, mean age 26.54 ± 3.65 years) and
70 healthy control women (mean age 27.84 ± 3.63 years) were investigated in
Vilnius city (Lithuania) in 2009-2011. A skinfold caliper device was used to
measure skinfolds thickness in 13 sites (biceps, triceps, midaxillary, subscapular,
chest, abdominal, suprailiac, thigh, knee and calf). Height, body mass and waist
circumference were measured. Bioelectrical impedance analysis using Genius
220 was performed to measure fat mass. Glucose, insulin, C-reactive protein
(CRP) and lipids tests were assessed by standard techniques.

Results
BMI (21.10 ± 2.02 vs 21.05 ± 1.65 kg/m², P = 0.876) and waist circumference
(69.03 ± 4.94 vs 68.73 ± 4.44 cm, P = 0.689) did not differ between PCOS and
control groups.

Fat mass in lean women with PCOS was higher by 8.92 kg than in controls
(P < 0.0001). In women with PCOS arms’ skinfolds (triceps by 2.42 mm, biceps
by 5.49 mm and forearm by 2.36 mm) and trunk skinfolds (suprailiac by 4.36 mm
and subscapular by 2.51 mm) were thicker than in the controls (P < 0.05). The
arm-to-leg and trunk-to-arm skinfolds’ ratios confirmed predisposition to
accumulate adipose tissue in the upper part of the body in women with PCOS.

Fasting glycaemia and glycaemia 2 hours after of 75 g glucose intake,
triglycerides and total cholesterol-to-HDL ratio was higher, but HDL was
accumulate adipose tissue in the upper part of the body in women with PCOS.

Adipose tissue in PCOS women tends to accumulate in the upper part of the body:
on arms and trunk – which may be the distinguishing feature of PCOS women.

Conclusions
Fat mass in PCOS women is higher than healthy women

P575
Effect of resistin on LH and FSH stimulated steroidogenesis in porcine
ovarian follicles during estrous cycle
Agnieszka Rak-Mardyla & Anna Karpeta
Jagiellonian University, Cracow, Poland.

Resistin is a recently discovered 12.5 kDa cysteine-rich secreted polypeptide first
reported from rodent adipocytes and plays important role in the development of
insulin resistance and obesity. Recently, many investigators have linked resistin
to reproductive function. Resistin expression was observed in bovine and rat
ovaries and showed that resistin modulate granulosa cells function such as
steroidogenesis and proliferation, in basal state or in response to IGF-I in vitro.
Our previous study showed that resistin was present in porcine small, medium and
large follicles in prepubertal and normal estrous cycling animals. Additionally,
resistin could modulate ovarian steroid synthesis by increasing androgen
production. Porcine ovaries were collected from normal oestrus cycling crossbred
gilts (6-8 months of age; Large White and Polish Landrace) at a local abattoir.

Small (2-4 mm; SFs, n=6) and medium (4-6 mm; MFs, n=6) follicles collected at
days 4-6 and 10-12 respectively. Ovarian follicles were cultured in the presence or absence of resistin (at doses 0.1, 1 and 10) and LH (100 ng/ml) or FSH
(100 ng/ml) in MI99 medium cultured medium. After 24h, conditioned culture
medium were collected for steroid hormone secretion (progesterone-P4, androstendione-A4, testosterone-T, and oestradiol-E2) by enzyme immunoassay (EIA) but ovarian
follicles were homogenized to measurement expression of steroid enzymes
(3β-HSD, CYP17, 17β-HSD, and CYP19) by using immunoblot. Statistical
analyses were performed using GraphPad Prism 5 software. Data were analyzed
using a one-way analysis of variance (ANOVA) test, followed by Tukey’s
honestly significant difference (HSD) test. We observed that resistin increased
stimulated LH and FSH P4, and A4 secretion by up-regulating the steady state
levels of CYP11A1. 3β-HSD and CYP17A1, and 17β-HSD and had no effects on
E2 secretion and CYP19A1 expression in ovarian follicles. Direct effects of
resistin on steroidogenesis suggest that resistin is a new regulator of ovary
function in animals during estrous cycle.
DOI: 10.1530/endoabs.32.P575

P576
Relation of liver enzymes with indices of insulin resistance and
hyperandrogenism in different PCOS phenotypes
Djuro Macul1, Ivana Bozic Antic2, Dimitrios Pandis2, Jelica Bjekic-
Macut3, Danijela Vojnovic Milutinovic4, Olivera Stanojlovic4,
Biljana Kastratovic2, Milan Petakov1, Bojana Popovic1, Sanja Ognjanovic1,
Tamar Bogavac1, Tatjana Isailovic1, Valentina Elezovic1 & Dusan Ilic1
1Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical
Center of Serbia, Faculty of Medicine, University of Belgrade, Belgrade;
Serbia, 2Division of Endocrinology and Human Reproduction, 2nd
Department of Obstetrics and Gynecology, Aristotle University of
Thessaloniki, Thessaloniki, Greece; 3Clinical-Hospital Center ‘Bezanija
kosa’, Belgrade, Serbia; 4Institute for Biologic Investigations ‘Simiša
Stanковic’, Belgrade, Serbia; 5Institute for Physiology, Medical Faculty,
University of Belgrade, Belgrade; Serbia, 6Clinic for Obstetrics and
Gynecology, Clinical Center of Serbia, Faculty of Medicine, University of
Belgrade, Belgrade, Serbia.

Introduction
Insulin resistance is a common discriminator for a variety of chronic disorders
including polycystic ovary syndrome (PCOS) and non-alcoholic fatty liver
disease (NAFLD). It has recently been hypothesized that PCOS itself might be a
risk for developing NAFLD.

Methods
We analyzed 560 women with PCOS (BMI: 31.19 ± 6.75 kg/m²; age: 25.62 ± 6.05
years) diagnosed on the basis of ESHRE/ASRM criteria. The subjects were divided and compared according to the clinical phenotype: phenotype A: anovulation + hyperandrogenism + polycystic ovaries (n=324), phenotype B: anovulation + hyperandrogenism (n=144), phenotype C: hyperandrogenism + polycystic ovaries (n=45), phenotype D: anovulation + polycystic ovaries (n=47). Subgroups did not differ in BMI (P = 0.085) but there was significant difference in age (P = 0.011) so all statistical analyses were done
with adjustment for age. During follicular phase of menstrual cycle fasting blood
samples were collected for determination of glucose, insulin, bilirubin, aspartate
aminotransferase (AST), alanine aminotransferase (ALT), testosterone and
SHBG. FAI and HOMA-IR were calculated using standard formula.

Results
There was no significant difference in levels of liver enzymes between different
PCOS phenotypes (AST: P = 0.72; ALT: P = 0.34). Significant correlations
existed in phenotypes A, B and C between ALT and insulin (r = 0.35, P < 0.001; r = 0.32, P < 0.001; r = 0.34, P = 0.02 respectively) and ALT and HOMA-IR
(r = 0.34, P < 0.001; r = 0.32, P < 0.001; r = 0.35, P = 0.02 respectively), but there
was no correlation between these parameters in phenotype D. There were no
significant correlations between liver enzymes, testosterone and SHBG. When
analyzed according to FAI, in PCOS subgroup with FAI≥6 significant
relations were found between ALT and insulin (r=0.39, P<0.001) and ALT and HOMA-IR (r=0.38, P<0.001), while there were no significant
correlations between those parameters in subgroup with FAI<6.

Conclusion
PCOS phenotypes had different influence towards development of NAFLD.
Besides insulin resistance, it seems that androgens may additionally influence
development of liver disease.

DOI: 10.1530/endoabs.32.P576
P577
The hinge region of the lutropin receptor mediates different activation mechanisms: CG induces trans- and LH only cis-initialization
Paul Grzesik1, Annika Kreuchwig1, Anke Teichmann1, Jens Furkert1, Claudia Rutz1, Burghard Wiesner1, Gunnar Kleinau3, Ralf Schülein1, Jörg Gronoll1 & Gerd Krause1
1Leibniz Institut für molekulare Pharmakologie (FMP), Berlin, Germany, 2Reproduktionsmedizin und Andrologie, Universität Münster, Münster, Germany, 3Charité-Berlin, Berlin, Germany.

The lutropin receptor (LHR) is associated with reproduction and becomes activated by chorionadotropin (CG) or lutropin (LH) resulting in different physiological functions with regard to differing signaling cascades. The underlying mechanisms in receptor/hormone interaction are not yet understood. CG is known to induce trans-activation at LH oligomers (activates a second receptor), but details of LH mechanisms were not clarified yet. To study this issue, we here used the LHR variant lacking exon 10 (hLHR-delEx10) encoding 27 residues of the extracellular hinge region, because it was previously reported that in contrast to CG, LH-induced cAMP accumulation is decreased at hLHR-delEx10. We, therefore, hypothesized a potential relation between the hinge region and differentially initialized signal induction by the hormone subtypes. Since coexpression of binding- and signaling-deficient LHR mutants can restore CG-induced function, we assumed that CG maintains full signaling capacity at hLHR-delEx10 by trans-activation, while the lack of exon 10 might disturb trans-activation of LH. Thus, we coexpressed the hLHR-delEx10 and the hLHR-Lys605Glu mutant – in which signaling is abolished – with the binding-deficient mutant hLHR-C131R. In contrast to CG, LH only activates hLHR via cis- (bound protomer), but not via trans-activation. Structure predictions and advanced structural models suggest that exon 10 encoded and consecutive residues likely form two helical elements. In accordance to this, block-wise poly-alanine (structure preserving) mutations within this region showed no effect on signaling. Surprisingly, the structure disturbing double-proline mutant LHR-303P/305P within exon 10 has – in contrast to hLHR-delEx10 – no impact on LH, but on CG signaling, while a single proline mutation after exon 10 showed wild type-like functions. In conclusion, our complementary structural and functional insights support the hypothesis that the hinge region links the hinge region with the LHR protomer), but not via trans-activation.

DOI: 10.1530/endoabs.32.P577

P578
AMHR2 polymorphism and risk for polycystic ovary syndrome: relationship to gonadotropin levels
Neoklis Georgopoulou1, Eleni Karagiannidou1, Vasiliki Koika1, Nikolaos Roupas1, Anastasia Armeni1, Dimitra Marioli1, 2Efthathios Papadakis1, Corine Welt1 & Dimitrios Panidis1
1Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, University of Patras Medical School, Patras, Achaia, Greece; 2Division of Endocrinology and Human Reproduction, Second Department of Obstetrics and Gynecology, Aristotle University of Thessaloniki, Thessaloniki, Greece; 3Reproductive Endocrine Unit, Department of Medicine, Massachusetts General Hospital and Harvard Reproductive Endocrine Sciences Center, Harvard Medical School, Boston, Massachusetts, USA.

Introduction
The polycystic ovary syndrome (PCOS) is a common and complex disease without a clear pattern of inheritance. There is evidence that PCOS is affected by both genetic and environmental factors, but there is no single and unambiguous explanation for its pathogenesis. Anti-Müllerian-inhibiting hormone (AMH) has an inhibitory effect on FSH-stimulated follicle growth and it has also been shown that serum AMH levels are higher in women with PCOS than in normal fertile women. The elevated AMH levels may reflect abnormalities at the AMH receptor. The current study examined the AMH receptor 2 (AMHR2) —482 A>G polymorphism (rs2002555) in a large cohort of PCOS women. The large number of the participants as well as their ethnic homogeneity enhanced the ability to detect a potential correlation between this polymorphism and the PCOS syndrome.
PPAR-γ down-regulated resistin expression in rodents. The aim of the study was to analyze i) basal resistin and PPAR gene and protein expression and ii) effect of resistin and rosiglitazone on PPAR-γ gene and protein expression. Porcine ovaries were collected from normal prepubertal gilts (6–8 months of age; Large White and Polish Landrace) at a local abattoir. Small (2–4 mm; SFs, n = 6), medium (4–6 mm; MFs, n = 6) and large (8–12 mm; LFs, n = 6) follicles collected at days 4–6, 10–12, and 16–18 respectively. Ovarian follicles were cultured in the presence or absence of resistin (at doses 0.1, 1 and 10 ng/ml) or rosiglitazone (at doses 25 and 50 μM, diluted in DMEM) in M199 medium. At 24 h, conditioned culture media were removed but ovarian follicles were homogenized to measurement expression of PPAR-γ receptor by immunoblot and real-time PCR in all follicles. Additionally, basal resistin and PPAR γ gene and protein expression were also determined. Statistical analyses were performed using GraphPad Prism 5 software. Data were analyzed using a one-way analysis of variance (ANOVA) test, followed by Tukey’s honestly significant difference (HSD) test. We demonstrated that basal PPAR γ was increased with maximum expression in LFs but resistin expression was unchanged in ovarian follicles. Moreover, both resistin and rosiglitazone increased PPAR-γ expression. In conclusion, our study provides the novel evidence interaction among resistin and PPAR γ in the pig ovary and suggest involvement of this receptor in the control of key ovary functions.

DOI: 10.1530/endoabs.32.P580

P581
Differences in adrenocortical steroid response to ACTH in women with post-adolescent severe acne and PCOS
Nese Cinar1, Fatma Cetinozman1, Duygu yazgan Aksoy1, Gonca Elcin1 & Bulent O Yildiz1
1Hacettepe University School of Medicine, Department of Endocrinology and Metabolism, Ankara, Turkey; 2Hacettepe University School of Medicine, Department of Dermatology, Ankara, Turkey.

Introduction
Increased adrenocortical production appears to be associated with acne and hirsutism in PCOS. However, the etiological role of androgens in the pathogenesis of acne per se is far from being clear. In the present study, we aimed to evaluate adrenocortical function in women with post-adolescent severe acne in comparison with patients with PCOS and healthy women.

Design
The study included 32 women with post-adolescent severe acne, 32 women with PCOS and 32 age and BMI-matched healthy controls (age 17–34 years, BMI: 20.8 ± 1.9 kg/m²). Women with acne did not have hirsutism/biochemical hyperandrogenism or ovulatory dysfunction whereas all PCOS patients had androgen excess and ovulatory dysfunction. Measurements included basal testosterone (T), SHBG and DHEAS levels and serum 17-hydroxprogesterone (17-OHP), androstenedione (A4), DHEA and cortisol levels in response to ACTH stimulation.

Results
T, FAI, DHEAS levels, basal and AUC (area under the value) curves for A4 were significantly higher in PCOS than women with acne and controls (P < 0.05 for all) whereas in controls the basal A4 was lower than in other groups. Women with PCOS and severe acne had significantly and similarly higher AUC values of 17-OHP compared to controls (P > 0.05).

Conclusion
Women with isolated post-adolescent severe acne do not have increased levels of adrenal androgens basally or in response to ACTH. However, these women have similar secretion pattern of 17-OHP with PCOS patients suggesting increased enzymatic activity in this pathway.

DOI: 10.1530/endoabs.32.P581

P582
Ovarian function is associated with obesity in very long-term female survivors of childhood cancer
Wendy van Dorp1,2, Karin Blijdorp3,3, Joop Laven2, Rob Pieters1, Jenny Visser4, Aart-Jan van der Lely1,2, Sebastian Neggler1,3 & Marry van den Heuvel-Eibrink1
1Department of Pediatric Oncology/Hematology, Erasmus MC-Sophia Children’s Hospital, Rotterdam, The Netherlands; 2Department of Gynecology and Obstetrics, Subdivision Reproductive Medicine, Erasmus MC–University Medical Center, Rotterdam, The Netherlands; 3Department of Medicine – section Endocrinology, Erasmus MC–University Medical Center, Rotterdam, The Netherlands; 4Department of Internal Medicine, Erasmus MC–University Medical Center, Rotterdam, The Netherlands.

Introduction
Obesity and gonadal dysfunction are major side effects of treatment in adult childhood cancer survivors. In the general population, obesity has a negative influence on female fertility. The aim of the study was to evaluate whether obesity and serum insulin are associated with decreased ovarian reserve markers in childhood cancer survivors.

Methods
We performed a retrospective single-center cohort study in 191 adult female survivors of childhood cancer. Median age at follow-up was 27.1 (range 17.7–50.0) years and median follow-up time was 18.8 (2.3–48.8) years. Outcome measures were serum levels of anti-Mullerian hormone (AMH) and total follicle count (FC) and – if measured during early follicular phase or anovulatory – antral follicle count (AFC). Potential risk factors were body mass index (BMI), body composition measures, determined by dual energy X-ray absorptiometry (total fat percentage, lean body mass and visceral fat percentage) and fasting insulin. Multiple linear regression analysis, adjusted for potential confounders, was used to evaluate the associations between potential risk factors and serum AMH and FC.

Results
Lower serum AMH was found in obese subjects (β (%) = −49, P = 0.007), and in subjects with fasting insulin in the highest tertile (β (%) = −43, P = 0.039). Total fat percentage tends to be associated with serum AMH (β (%) = −2.1, P = 0.06). Survivors in the highest tertile of insulin had significant lower FC than survivors in the lowest tertile (β = −6.3, P = 0.013). BMI and other measures of body composition were not associated with FC. Correlation between serum AMH and AFC was r = 0.32 (P = 0.08).

Conclusions
Obesity and insulin resistance are associated with gonadal damage, as reflected by decreased AMH and reduced FC in adult survivors of childhood cancer. In contrast to its highly predictive value for AFC in the healthy female population, serum AMH does not seem to correlate as well with AFC in childhood cancer survivors.

DOI: 10.1530/endoabs.32.P582

P583
New endocrine and intracellular regulators of ovarian functions
Alexander V S
Animal Production Research Centre Nitra, Luzianky, Slovakia.

This is the review of original data concerning the role of some metabolic hormones (GH, leptin, ghrelin, obestatin), growth factors (IGF-I, IGFIRPs, EGF, thrombopoietin), intracellular mediators of their action (cyclic nucleotides, protein kinases, MAPK, CDK, transcription factors, CREB, STAT-1, p53 and related cDNA, siRNA and mRNA gene constructs) on basic ovarian functions (cell proliferation, apoptosis, secretion, oogenesis, ovulation, production and viability of pups) in different species (pig, rabbit, humans and chicken). These hormonal and intracellular regulators are able to control apoptosis, proliferation and secretory activity in porcine, rabbit, human and chicken ovarian cells and maturation of porcine oocytes and cumulus oophorus in vivo and in vitro, as well as to suppress or promote the response of ovarian cells to other hormones. Insulinoma-blockade of these hormones prevented their effects. Effects of hormones on ovarian cells were associated with changes in protein kinases and transcription factors in such cells, whilst blockers of kinases prevented or promoted hormones action. Transfection of granulosa cells with gene constructs for some transcription factors affected ovarian cell functions and modify hormones action. Down-regulation of approximately 1/3 known protein kinases by specific siRNA constructs resulted decrease in accumulation of these kinases within granulosa cells and changes in expression of kinase-dependent transcription factors, markers of cell proliferation, apoptosis and release of steroid hormones and IGF-I. Transfection of granulosa cells with constructs up and down regulating expression of some mRNAs are able to alter ovarian cell proliferation, apoptosis, as well as the hormone release. In vivo experiments demonstrated that leptin, IGF-I, steroid hormones and some regulators of PKA, MAPK and CDK could be used to predict reproductive efficiency, for direct in vitro control of maturation of oocytes and for in vivo stimulation of reproduction. Therefore, metabolic hormones, growth factors and intracellular regulators and mediators of their action (protein kinases, transcription factors, siRNAs, mRNA) can be used for characterization of state of ovarian cells, for identification signaling pathways controlling reproductive processes, as well as for prediction and control of basic ovarian cell functions.

DOI: 10.1530/endoabs.32.P583
Deletions of TCF2 gene in Rokitansky syndrome (MRKH): a new candidate gene? About new two cases
Deborah Ancelle1, Annie Claude Hecart1, Dominique Gaillard2, Eric Bertin3 & Brigitte Delemer1
1Department of Endocrinology, University Hospital, Reims, France; 2Department of Genetics, University Hospital, Reims, France.

Introduction
MRKH syndrome is a rare congenital disease, which affects 1/5000 female births. It is usually diagnosed in the course of primary amenorrhea investigation. Characteristics are mullerian agenesis with 46XX karyotype. Only Wnt4 gene (1) was involved in a few cases of MRKH with hyperandrogenism. We describe two new cases associating MRKH syndrome and complete deletion of TCF2 gene in the heterozygous state, this gene is also involved in monogenic diabetes type 5.

Case 1
Seventeen year old, primary amenorrhea, karyotype 46XX, normal puberty. Clinical examination: 3 cm vagina, MRI: absence of uterus, normal ovaries.

Case 2
Six years old left kidney atrophy, 14 years insulinated diabetes, diagnosis of primary amenorrhea at 17 years old, karyotype: 46XX, normal puberty. At clinical examination: utero-vaginal aplasia. Occurrence of renal deficiency and increase level of liver enzymes during follow up.

Molecular biology
Complete deletion of TCF2 gene in the heterozygous state in these two cases.

Conclusion
TCF2 gene is involved in MODY 5 diabetes, encoding HNF1B a nuclear transcriptional factor expressed in several organs (liver, lung, pancreas, kidney and genital tract). 18% of women with TCF2 mutations have kidney and genital tract abnormalities (bicornuate uterus). To date only three cases have been reported, two siblings in 1999 (4) and a 24 weeks fetus in 2008 (5). It was a partial TCF2 deletion in heterozygous state in these three MRKH syndrome. With this two new cases associating MRKH syndrome and complete TCF2 deletions in the heterozygous state, with an insignificant renal cyst in one case, we suggest that this gene should be tested, regarding it’s implication during the follow up (renal failure, diabetes, liver enzymes).

References

DOI: 10.1530/endoabs.32.P584

Thrombosis in polycystic ovary syndrome: a marker of thrombosis
Mubeena Aziz1, Johannes J Sidelmann 2, Sven O Skouby 3 & Jens Faber4
1Department of Obstetrics/Gynecology, Herlev University Hospital, Herlev, Denmark; 2Unit for Thrombosis Research, Institute of Public Health, University of Copenhagen, Herlev University Hospital, Faculty of Health Sciences, University of Copenhagen, Herlev, Denmark; 3Department of Endocrinology, Herlev University Hospital, Faculty of Health Sciences, University of Copenhagen, Herlev, Denmark.

Background
Polycystic ovary syndrome (PCOS) is clinically associated with increased risk of CVD. Thrombin generation (TG) is a measure of the thrombotic potential. This can be expressed as endogenous thrombin potential (ETP) representing the total amount of generated active thrombin over the time ($mmol/l/min$). ETP is considered the most predictive parameter of thrombosis and is associated to both venous and arterial thrombotic disease. Setting: PCOS women prospectively referred to three Danish Gynecological clinics due to infertility, hirsutism and oligo-amenorrhea.

Materials and methods
One hundred and forty-eight PCOS women diagnosed according to the Rotterdam criteria, mean age 27 years (range 18–40). Measurements: BMI, plasma TG, hCRP, PAI-1, HOMA-IR, body composition (DXA) and urinary-albumin/creatinin. The calibrated automated thrombogram was used to measure TG.

Results
ETP levels were divided into tertiles: Total and free testosterone, u-albumin/creatinin did not correlate to ETP. The correlation to total fat mass (TFM) seemed equal to both android and gynoid fat. ETP did not correlate to number or combinations of the Rotterdam criteria. In a univariate analysis, ETP correlated to the majority of the above-mentioned parameters. In a multivariate analysis including TFM, HOMA-IR, hCRP, total and LDL-cholesterol, triglycerides, ETP was independently associated with TFM and total cholesterol ($β=0.358, P=0.025; β=0.482, P=0.022$ respectively).

Conclusion
Increasing ETP is associated with a number of parameters traditionally associated with increased risk of CVD in PCOS. This association seems mainly driven by total FM and cholesterol in PCOS. The Rotterdam criteria were unable to detect this signal of potentially increased risk of thrombosis.

DOI: 10.1530/endoabs.32.P585

The combination of genetic variants in the FSHR and FSHB genes affect serum FSH in women of reproductive age
Valeria Mironondo1, Antonio La Marca2, Enrico Alviggi3, Gianni Ruvoli1, De Placido Giuseppe4, Massimo Candiani5, Ettore Cittadini3, Francesca De Michele1, Valeria Catellani1, Annibale Volpe2 & Manuela Simon1
1Unit and Chair of Endocrinology and Metabolism, Department of Biomedicine, Metabolism and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy; 2Mother–Infant Department, University of Modena and Reggio Emilia, Modena, Italy; 3Centro Natalita`, Mother–Infant Department, Vita-Salute University, Milan, Italy; 4Department of Obstetrics, Gynecology, Urology and Reproductive Medicine, Federico II University of Naples, Naples, Italy; 5Reproductive Medicine Center, University of Palermo, Palermo, Italy.

Introduction
The relationship between SNPs of the FSHR gene and serum FSH has not been completely clarified. Genetic variants of the FSHB gene have been associated to variation in gene transcription and to serum FSH levels in men. An interesting joint effect of both FSHB $–211G>T$ and FSHB $2039 A>G$ on male reproductive parameters has been recently observed. No data have been published on the effect of the FSHB $–211G>T$ in combination with the FSHB $2039 A>G$ in women.

Description of methods
To investigate the effect of FSHB $–211G>T$ together with the FSHB $2039 A>G$ on serum FSH in women we conducted a prospective study including 193 healthy eumenorrhoic women of reproductive age. In all women, early follicular phase FSH and AMH were measured by commercial assays and antral follicle count was measured by transvaginal ultrasound. Genomic DNA was purified from total peripheral blood and genotyping for the two SNPs was performed by HRM technique.

Results
No significant gradients of increasing or decreasing day 3 FSH across the FSHB $2039 AA/AG/GG$ and FSHB $–211 (GG/GT/TT)$ genotypes, respectively, were observed. When women were stratified according to the FSHB $2039$ and the FSHB $–211$ genotypes a statistically significant reduction of day 3 FSH was shown in the group of women with the FSHB $–211 GT/TT/FSHBR2039 AA$ genotype compared to the FSHB $–211 GG/FSHBR2039$ GG genotype.

Conclusion
The reduction of day 3 FSH evidenced in the group of women with the FSHB $–211 GT + TT/FSHBR2039$ AA genotype confirms a possible additive effect of the different SNPs in FSHR and FSHB on regulating serum FSH in women.

DOI: 10.1530/endoabs.32.P586
The hypothalano-pituitary-adrenal axis sensitivity in women with polycystic ovary syndrome

Dusan Ilic1, Djuro Macut2, Ivana Bozic Antic3, Jelica Bjekic-Macut2, Danijela Vojnovic Militinovic4, Biljana Kastratovic5, Bojana Petakov2, Sanja Ognjanovic1, Tamara Bogavc2, Tatjana Isailovic2, Valentina Elezovic & Svetozar Damjanovic1

1Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Belgrade, Serbia; 2Clinical-Hospital Center “Bežanjska kosa”, Belgrade, Serbia; 3Institute for Biologic Investigations, Sima Stanovich2, Belgrade, Serbia.

Introduction
It has been shown that most women with polycystic ovary syndrome (PCOS) have increased adrenal androgen production, enhanced peripheral metabolism of cortisol and elevated in urinary excretion of its metabolites. Simultaneously, this increased cortisol clearance was shown to be followed by a compensatory overdrive of the hypothalano-pituitary-adrenal (HPA) axis. The aim of this study was to determine HPA axis sensitivity in women with PCOS.

Methods
We studied 65 non-obese women with PCOS (group PCOS: 24.7±4.0 years; 22.5±3.3 kg/m²) aged 20 years and BMI matched healthy women (group controls: 27.3±5.3 years; 21.9±1.9 kg/m²). PCOS was diagnosed using ESHRE/ASRM criteria. In all subjects during follicular fase of menstural cycle levels of cortisol, ACTH, DHEAS, testosterone, androstenedione and 17-OH-progesterone were determined. Overnight dexamethasone test with 0.5 mg was performed with subsequent determination of morning cortisol.

Results
PCOS and controls significantly differed in SHBG (40.9 ±22.9 vs 65.9 ±31.2 nmol/L, P = 0.021) and FAI (9.1 ±8.1 vs 3.6 ±1.4%, P = 0.018), while DHEAS, 17-OH-progesterone, androstenedione, basal cortisol, ACTH did not differ between groups. PCOS supressed cortisol less than controls after 0.5 mg of dexamethasone (85.0 ±16.9 vs 93.3 ±3.2%, P = 0.001).

Conclusion
Lower HPA axis sensitivity women with PCOS with simultaneously normal basal cortisol and ACTH levels could be a mechanism for compensatory overdrive of HPA axis in this patients.

DOI: 10.1530/endoabs.32.P587

The assessment of metabolic derangements including metabolic syndrome in relation to the degree of hyperandrogenism in women with polycystic ovary syndrome

Jelica Bjekic-Macut2, Ivana Bozic Antic3, Dimitrios Panidis3, Danijela Vojnovic Militinovic4, Ivana Stanoljovic4, Milan Petakov2, Bojana Popovic2, Tamara Bogavc2, Sanja Ognjanovic1, Tatjana Isailovic2, Valentina Elezovic, Dusan Ilic1 & Djuro Macut2

1Clinical-Hospital Center “Bežanjska kosa”, Belgrade, Serbia; 2Clinical-Hospital Center “Bežanjska kosa”, Belgrade, Serbia; 3Institute for Biologic Investigations, Sima Stanovich2, Belgrade, Serbia.

Introduction
Polycystic ovary syndrome (PCOS) is associated with a higher risk for development of metabolic syndrome (MS). In this study, we evaluated the degree of metabolic disorders in women with PCOS and different degree of hyperandrogenism (HA).

Methods
We analyzed 234 women with PCOS (group PCOS: BMI: 22.4 ±3.6 kg/m²; age: 24.8 ±4.7 years) diagnosed on the basis of ESHRE/ASRM criteria, and 45 healthy BMI-matched women who comprised the control group (group controls; BMI: 21.3 ±3.2 kg/m²; age: 28.3 ±4.9 years). Women with PCOS were divided into three subgroups according to the presence of HA: i) with biochemical HA (n = 123), ii) with clinical HA (n = 61), and iii) without clinical or biochemical HA (n = 50). In all subjects, basal blood samples were collected in follicular phase of menstrual cycle for determination of glucose, insulin, total cholesterol (TC), HDL, LDL, triglycerides, apolipoproteins A1, A2, B and E, lipoprotein(a), C-reactive protein (CRP) and uric acid. HOMA index was calculated using standard formula, and lipid ratios TC/HDL, LDL/HDL, triglycerides/HDL, ApoB/ApoA1 were determined. MS was diagnosed according to JIS criteria.

Results
In comparison to PCOS subgroup B and C, PCOS subgroup A had higher triglycerides (P <0.001 and P = 0.012) and CRP (P = 0.032 and P = 0.022), lower ApoB/ApoA1 (P = 0.045 and P = 0.007), and higher TC/HDL ratio (P = 0.02 and P = 0.007) and triglycerides/HDL ratio (P <0.001 and P = 0.001), respectively. PCOS subgroup A in comparison to PCOS subgroup C had significantly lower HDL (P <0.001) and higher ApoB/ApoA1 ratio (P = 0.045). There was higher prevalence of MS in PCOS subgroup A (21%) in comparison to groups B (3%) and C (5%), P <0.001.

Conclusion
PCOS women with biochemical HA had unfavorable lipid profile and higher prevalence of MS than PCOS women without hyperandrogenemia.

DOI: 10.1530/endoabs.32.P589

Gynecological aspects of prolactinoma

Haifa Abdesselem, Emma Haouat, Leila Ben Salem, Hajer Kandara, Zinet Turki & Claudio Ben Slama

National institute of nutrition, Tunis, Tunisia.

Prolactinoma is a pitutitary adenoma producing prolactin. Central hypogonadism is a major consequence of prolactinoma leading, in women, to menstrual troubles.
and infertility. The aim of this study was to specify gynecological characteristics of prolactinomas. Patients
This retrospective study included 28 female patients with prolactinoma. Mean age at diagnosis was 35.46 years (ext: 20–78). Mean serum prolactin level was 3442.4 mg/ml (ext: 31.9–76 915). Mean size of adenoma was 17.26 mm (ext: 5–60). It was a microadenoma (< 1 cm) in 32.1% (n = 9) and a macroadenoma in 67.9% (n = 19) of cases. Results
At diagnosis, history taking revealed a pregnancies average of 1.67 (ext: 0–8) for spontaneous pregnancies and 0.13 (ext: 0–2) for induced ones. Abortions average was 0.30 (ext: 0–2). Parity average was 1.24 (ext: 0–5). Among patients, 78.9% were not using any contraception. Intruterine device (IUD) was used in 15.8% of patients and progesterin in 5.3% of them. Diagnostic circumstances were galactorrhea in 15% (n = 3), amenorrhea-galactorrhea in 35% (n = 7), menstrual disturbance in 30% (n = 6) and tumoral syndrome in 20% of cases (n = 4). All patients were treated with dopamine agonists. No patient was treated by surgery. After diagnosis, hypogonadotropic hypogonadism was persistent in 20% of patients (n = 4). Fifty per cent of women were using IUD as contraception, 33.3% had no contraception and 16.7% was on progesterin. Thirteen pregnancies occurred in seven patients (four microadenomas and three macroadenomas). The number of pregnancies by patient was 1, 2 and 3 in respectively 21.4% (n = 3), 14.3% (n = 2) and 14.3% (n = 2) of patients. During pregnancy, 66.7% of women (n = 4) used dopamine agonists with a favorable outcome. Two of them had a macroadenoma.
Conclusion
These results highlight the huge gynecological impact of prolactinoma. A delayed diagnosis or insufficient treatment of this affection may lead to infertility or complicated pregnancies.
DOI: 10.1530/endoabs.32.P590

P591
Levonorgestrel inhibits human endometrial cell proliferation through the up-regulation of gap junctional intercellular communication via the increased expression of Connexin43 and the nuclear translocation of its Ser255 phosphorylation
Xiaomiao Zhao1, Xuelian Tang2 & Meiqing Xie1
1Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, Guangdong, China; 2Shenzhen Maternity and Child Care Centers, Southern Medical University, Shenzhen, Guangdong, China.

Context
Gap junction intercellular communication (GJIC) and its constructed protein Connexin (Cx) participates in cell apoptosis and tumorigenesis. Our clinical studies demonstrated that a levonorgestrel (LNG)-releasing intrauterine system can reverse atypical endometrial hyperplasia. Objective
This study assesses whether LNG exerts anti-proliferation effects on human endometrial cells through changes in the GJIC function and Cx43 expression. Methods
The cell proliferation and apoptosis of human endometrial stromal cells (HESCs) and glandular cells (HEGCs) treated with LNG in a dose- and time-dependent manner. GJIC change and further total along with serine 368 and 255 phosphorylated Cx43 were measured.
Results
In all, 5 × 10−5 mol/l LNG revealed a time-dependent inhibition of cell proliferation and an increase of apoptosis in both HESCs and HEGCs. Furthermore, these cells demonstrated a significant GJIC enhancement upon treatment with 5 × 10−5 mol/l for 48 h. The effects of LNG were most noticeable in HESCs rather than in HEGCs. Associated with these changes, LNG induced a relative increase in total Cx43 in a time-dependent manner but not Ser368 phosphorylated Cx43, which was measured in HESCs using western blot analysis. Furthermore, laser scanning confocal microscope confirmed the increased expression of total Cx43 in the cytoplasm and, interestingly, detected the nuclear translocation of Ser255 phosphorylated Cx43.
Conclusions
LNG likely inhibits the proliferation and promotes apoptosis in HESCs and HEGCs though an increase in gap junction permeability in vitro, which is achieved through the upregulation of Cx43 expression and the translocation of serine 255 phosphorylated Cx43 from the plasma to the nuclear compartment.
DOI: 10.1530/endoabs.32.P591

P592
Overnight 1 mg dexamethasone androgen suppression test is useful diagnostic tool in hyperandrogenism.
Urszula Ambrozik1, Anna Kępczyńska-Nyk1, Karolina Nowak1, Emilianna Morawka2, Michał Kunitzk1 & Tomasz Bednarski1
1Department of Endocrinology, Warsaw Medical University, Warsaw, Poland; 2Student Endocrine Circle, Warsaw Medical University, Warsaw, Poland; Invicta Fertility Clinic, Warsaw, Poland.

Introduction
Low dose dexamethasone (DEX) androgen suppression test (LDDAST) is considered a tool to distinguish between the sources of androgen excess and to exclude/confirm autonomy of androgen overproduction.

Aim
To assess whether 1 mg DST can be used instead of LDDAST.

Materials and methods
Thirty-three consecutive women with hyperandrogenism age 18–38 years underwent overnight 1 mg DEX androgen suppression test and LDDAST. Testosterone, androstendione, dehydroepiandrosterone sulfate were measured initially, after 1 mg DEX and after 2 days of 2 mg DEX. 50% of initial level was considered the cut off of suppression.

Results
All but three patients (91%) who achieved less than 50% suppression of testosterone after 1 mg DEX did not suppress testosterone after 2 mg. All who suppressed after 1 mg also suppressed after 2 mg. 100% women did not achieve the cut off of DHEAS suppression after 1 mg, but all achieved after 2 mg of DEX. All but three patients (91%) who suppressed androstendione of less than 50% after 1 DEX did not suppress after 2 mg. The percent of suppression was however borderline after 1 and 2 mg. All who suppressed after 1 mg also suppressed after 2 mg. Three patients without 50% suppression of testosterone after 1 mg DEX achieved the cut off after 1 and 2 mg of androstendione. Three patients who did not achieve the cut off in androstendione after 1 mg but did after 2 mg did not suppress testosterone after 1 and 2 mg and all had PCOS diagnosed.

Conclusions
1 mg DST with assessment of testosterone and androstendione can be used in outpatient fashion instead of 2 mg LDDAST. Suppression of androstendione after 1 mg DEX is complementary in case of lack of testosterone suppression after 1 mg DEX but presence after 2 mg. DOI: 10.1530/endoabs.32.P592

P593
Low dose oral contraceptive use and the risk of thrombosis in polycystic ovary syndrome
Safak Akin1, Nese Cinar1, Kadriye Aydin1, Umit Akman2 & Yahya Buyukasik2
1Hacettepe University, Faculty of Medicine, Department of Endocrinology and Metabolism, Ankara, Turkey; 2Hacettepe University, Faculty of Medicine, Department of Hematology, Ankara, Turkey.

Background and aim
Oral contraceptives (OC) are the mainstay of long-term treatment for women with polycystic ovary syndrome (PCOS). OC use is associated with increased risk of venous thromboembolism. The aim of the present study was to determine whether treatment with a low dose OC induce changes on coagulation and fibrinolysis in women with PCOS.

Materials and methods
Sixteen lean, normal-glucose tolerant patients with PCOS (mean age, 22.4 ± 2.4 years; mean BMI, 20.0 ± 2.5 kg/m2) and aged 16 years and BMI-matched healthy control women were included. All participants were non-smokers. At baseline, d-dimer, fibrinogen, activated partial thromboplastin time (APTT) and prothrombin time (PT) along with clinical, hormonal and biochemical measurements were performed in patients and controls. The studies were repeated in women with PCOS after 6 months of treatment with 0.03 mg ethinyl estradiol/3 mg drospirenone (EE-DRSP).

Results
All coagulation and fibrinolysis parameters were comparable between patients and controls at baseline. In women with PCOS; d-dimer, fibrinogen, APTT, and PT did not show a significant change after treatment (P = 0.16, P = 0.12, P = 0.81 and P = 0.56 respectively). EE-DRSP treatment resulted in a significant improvement in clinical/biochemical hyperandrogenism.

Conclusion
Our results suggest that 6 months use of EE-DRSP does not alter coagulation/fibrinolysis measured by clinical assays in lean women with PCOS.
DOI: 10.1530/endoabs.32.P593
P594
PCOS subphenotypes stratification reveals an apparent increase of metabolic syndrome frequency in patients with concomitant hyperandrogenism and menstrual irregularities.
Nicoleta Baculescu1, Serban Radian1, Illica Gussi2, Monica Gheorghiu1, Catalina Poiu1, Florin Grigorescu1 & Mihai Cocolescu1,2
1Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; 2Obstetrics and Gynecology Department, Cantacuzino Hospital, Bucharest, Romania.

Background PCOS-associated increased metabolic risk may be selective, owing to its heterogeneous nature. Identification of high-risk individuals could enable better studies and prevention of complications.

Aim To characterize the metabolic risk, as metabolic syndrome (MetS), of specific PCOS subphenotypes.

Subjects and methods Romanian PCOS (Rotterdam criteria) and 64 controls, 18–35 years. PCOS subphenotypes were defined: i) oligo-amenorrhoea (OA), hyperandrogenism (H), and polycystic ovarian morphology (P), OA–H–P (n = 143, 59.58%); ii) OA–H (n = 35, 14.83%); iii) H–P (n = 17, 7.08%) and iv) OA–P (n = 45, 18.75%). MetS was defined by harmonized IDF (2009) criteria. Total testosterone (TT), free-androgen index (FAI), insulin-sensitivity index (QUICKI) and SHBG are expressed as mean ± SEM and compared by ANCOVA, adjusting for BMI and age.

Results MetS prevalence was higher in OA–H–P and OA–H (28.24 and 34.8%) than in controls (10.4%) (P < 0.01). MetS frequencies (13.33 and 17.07%) of H–P and OA–P were not significantly different than controls or OA–H–P and OA–H. The OA–H–P and OA–H had higher TT (0.84 ± 0.02 and 0.89 ± 0.07 vs 0.67 ± 0.07 ng/ml, P < 0.05) and FAI (0.59 ± 0.48 and 0.78 ± 0.04 vs 2.88 ± 0.42, P < 0.01) and were more insulin-resistant (QUICKI = 0.325 ± 0.003 vs 0.355 ± 0.005, P < 0.05) than controls. Insulin-sensitivity did not differ significantly between the H–P and OA–P and controls (0.318 ± 0.013 and 0.321 ± 0.006 vs 0.352 ± 0.005, P > 0.05) than controls.

Conclusions The oligo-anovulatory hyperandrogenic PCOS have the highest MetS prevalence, suggesting they represent more severe PCOS. The ovulatory and normoandrogenic PCOS subphenotypes were not different than controls in MetS prevalence and insulin-sensitivity, suggesting less metabolic risk. However, direct comparison did not identify significant differences of the same parameters between these two and the more severe PCOS subphenotypes.

DOI: 10.1530/endoabs.32.P594

P595
Association of serum 25-hydroxyvitamin D and glucose levels in polycystic ovary syndrome
Gema López-Gallardo1, Pedro Rozas-Moreno1,2, Rebeca Reyes-García1,3, José María Tenías-Burillo1, María López-Iglesias1,4, Álvaro García-Manzanares1, Francisco-Javier Gómez1 & Ines Gómez-García1
1Division of Endocrinology, Mancha Centro Hospital, Alcázar de San Juan, Ciudad Real, Spain; 2Section of Endocrinology, University General Hospital Rafael Mendez, Lorca, Murcia, Spain; 3Support Unit Research, Mancha Centro Hospital, Alcázar San Juan, Ciudad Real, Spain.

Background Women with polycystic ovary syndrome (PCOS) frequently suffer from metabolic disturbances, in particular from pre-diabetes and diabetes. Conflicting results currently exists on the relationship between vitamin D and glucose metabolism. Hence, the aim of our study was to investigate the association of 25-hydroxyvitamin D (25(OH)D) levels and glucose tolerance in PCOS women.

Methods Cross-sectional study including 23 PCOS patients (mean age 27 years). 25(OH)D levels were measured by chemiluminescence (Cobas e 601 by ROCHE). Standard 75 g oral glucose tolerance test were performed. Results were analysed by SPSS 18.0.

Results Serum 25(OH)D concentrations was 18.8 ± 7.5 ng/ml. The prevalence of 25(OH)D insufficient (<30 ng/ml) and deficiency (<10 ng/ml) was 88 and 16% respectively.

Conclusions Three (12%), four (16%) and 16 (64%) women were patients with diabetes, glucose intolerance and normoglycemia respectively. PCOS women with glucose disturbance had lower 25(OH)D levels than PCOS women with normoglycemia (13.7 ± 7.5 ng/ml vs 20.13 ± 6.6 ng/ml, P < 0.05). In binary logistic regression analyses, 25(OH)D (OR 0.84, P < 0.05) was independent predictors of glucose metabolic alteration in PCOS women. We found significantly negative correlations of 25(OH)D level with basal glucose (r = −0.44, P < 0.05).

Conclusions Our results suggest that low 25(OH)D levels are associated with diabetes and glucose intolerance in PCOS women. Large intervention trials are warranted to evaluate the effect of vitamin D supplementation on glucose metabolic disturbances. PCOS women evaluate the effect of vitamin D supplementation on glucose metabolic disturbance in PCOS women. Glucose metabolic disturbances in PCOS women.

DOI: 10.1530/endoabs.32.P595

P596
Prevalence of prediabetes state is not equal in all phenotypes of polycystic ovary syndrome
Tahereh Madani, Roya Hosseini, Fariba Ramezanali, Nadia Jahangiri, Jila Ahmadi, Fateme Rastegar & Zahra Zolfaghari
Department of Endocrinology and Female Infertility, Reproductive Biomedicine Research Center, Royan Institute for Reproductive Biomedicine, ACECR, Tehran, Iran.

Introduction Polycystic ovary syndrome (PCOS) frequently accompanied by insulin resistance metabolic abnormality. There are limited data on metabolic complications in women belonging to the PCOS phenotypes as defined by the Rotterdam criteria. Our objective was to investigate the prevalence of impaired fasting glucose (IFG) metabolism and dyslipidemia between different phenotypes in Iranian infertile women with PCOS.

Methods We conducted a cross sectional study in our infertility outpatients clinic (Royan Institute), Tehran, Iran. A total of 633 women with PCOS according to Rotterdam criteria were studied (February 2011–September 2012). All subjects underwent blood samples for fasting glucose, lipids, reproductive hormones and a transvaginal ultrasound. Subjects were divided into following four different phenotypes: A) oligomenorrhea+hyperandrogenism + PCO, B) oligomenorrhea+hyperandrogenism, C) hyperandrogenism + PCO, and D) oligomenorrhea + PCO. Variables were compared between these phenotypes.

Results The mean age was 28.7 ± 4.5 years. Mean duration of infertility was 7.4 ± 4.4 years, 1.3% were infertile, mean BMI was 26.7 ± 3.7, 13.1% had IFG and 71.7% had high-density lipoprotein (HDL) cholesterol <50 mg/dl. Prevalence of IFG in different phenotypes of PCOS were 11.9, 33.3, 13.5 and 8.6% in A, B, C and D phenotypes respectively (P = 0.041). 75.6%, 77.8%, 70.3% and 67.0% in A, B, C and D phenotypes respectively had HDL cholesterol <50 mg/dl (P = 0.01). There was no statistically significant differences in other lipid profiles between different phenotypes of PCOS patients.

Conclusions Results of this study shows the prediabetes state and one the important cardiovascular risk factors – low HDL cholesterol – are more prevalent in B phenotype of PCOS. Classification of the metabolic complications for each phenotype will provide a guide for screening of metabolic risks of PCOS and may help to optimal treatment of these complications.

DOI: 10.1530/endoabs.32.P596

P597
Metabolic features in patients with polycystic ovary syndrome (PCOS) during different stages of reproductive life
Teresa Sir-Petermann, Amanda Ladron de Guevara, Barbara Echiburu, Nicolas Crisosto, Natalie Vantman, Cecilia Pereira, Francisco Perez-Bravo & Jose Galgani
University of Chile, Santiago, Chile.

Polycystic ovary syndrome (PCOS) is an important metabolic and reproductive disorder which confers substantially increased risk for type two diabetes and metabolic syndrome (MS). Our aim is to characterize the metabolic profile, insulin sensitivity (IS) and insulin secretion in control (Cw) and PCOS women
(PCOSw) during different stages of reproductive life (S1: 18–35 years old, S2: 36–44 years old, S3: 45–55 years old). A total of 131 Cw and 120 PCOSw were included, distributed as follows: S1: 69 Cw and 78 PCOSw, S2: 46 Cw and 40 PCOSw, S3: 16 Cw and 11 PCOSw. Clinical and anthropometric characteristics were evaluated. In both groups, a 2 h, 75 g OGTT was performed with measurement of glucose, insulin and lipids. HOMA-IR, insulin sensitivity index (ISI) composite, HOMA-beta, insulinogetic index and area under the curve for glucose and insulin were calculated. MS was evaluated according to the modified NCEP ATP III criteria. Chronological age, BMI, anthropometrics and fasting glucose were similar between Cw and PCOSw in the three study periods; 2-h glucose increased with age in PCOSw. Stage 1 and 2 PCOSw showed a higher prevalence of hypertension, hypercholesterolemia and hypertriglyceridemia compared to Cw.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Cw</th>
<th>PCOSw</th>
<th>Cw</th>
<th>PCOSw</th>
<th>Cw</th>
<th>PCOSw</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISI composite</td>
<td>3.5 (2.3–5.4)</td>
<td>3.9 (3.0–5.4)</td>
<td>3.5 (2.3–5.4)</td>
<td>4.9 (3.0–6.4)</td>
<td>3.5 (2.3–5.4)</td>
<td>4.9 (3.0–6.4)</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>5.8 (4.6–6.9)</td>
<td>6.5 (4.6–7.6)</td>
<td>5.8 (4.6–6.9)</td>
<td>7.5 (5.6–8.6)</td>
<td>5.8 (4.6–6.9)</td>
<td>7.5 (5.6–8.6)</td>
</tr>
<tr>
<td>Insulinogetic index</td>
<td>2.9 (2.1–4.6)</td>
<td>3.2 (2.1–4.5)</td>
<td>2.9 (2.1–4.6)</td>
<td>3.4 (2.2–5.0)</td>
<td>2.9 (2.1–4.6)</td>
<td>3.4 (2.2–5.0)</td>
</tr>
<tr>
<td>AUC insulin</td>
<td>2096 (1577–2639)</td>
<td>2306 (1789–3000)</td>
<td>2096 (1577–2639)</td>
<td>2306 (1789–3000)</td>
<td>2096 (1577–2639)</td>
<td>2306 (1789–3000)</td>
</tr>
</tbody>
</table>

The present study shows that during reproductive age, PCOSw are more affected metabolically than Cw. Nevertheless during the perimenopausal period, Cw are metabolically more perturbed showing a similar metabolic profile to PCOSw.

Endocrine Abstracts (2013) Vol 32

P598

Association of thyroid autoimmunity and thyroid dysfunction with obstetric antiphospholipid syndrome

Svetlana Jelic1,2, Ljudmila Stojanovich1 & Dragomir Marisavljevic1,2

1Bezanijska kosa Clinical Hospital Center, Belgrade, Serbia; 2School of Medicine, University of Belgrade, Belgrade, Serbia.

Background

The association of antiphospholipid syndrome (APS) with various endocrine disorders is already known. However, data on the influence of thyroid autoantibodies and/or disorders of thyroid function on the expression of classical APS manifestations are rather limited.

Objectives

The aim of this investigation was to evaluate the impact of thyroid autoimmunity and dysfunction on frequency of recurrent miscarriages in patients with primary APS (pAPS) manifestations are rather limited.

Methods

The study included 62 female patients with pAPS (mean age 43.32 ±11.10 years), classified according to the category of antiphospholipid antibodies (aPL) into four groups: I (with more than one aPL) – 41 patients (66%); Ia (isolated presence of lupus anticoagulant) – five patients (8%); Ib (isolated presence of anticoagulant antibodies) – 12 patients (19.5%) and Ic (isolated presence of anti-beta two GPI antibodies) – four patients (6.5%). All patients were screened for the presence of thyroid autoimmunity (anti-thyroglobulin antibody (TgAb), anti-thyroid peroxidase antibody (TPOAb) and thyroid receptor antibody (TRAb)) and thyroid dysfunction (thyroid stimulating hormone (TSH) and free thyroxine (T4)). Data on recurrent miscarriages were obtained from the patients’ medical records.

Results

Recurrent miscarriages were documented in 68% of the category I patients, all patients in the category Ia, 67% of the category Ib patients and 50% of those from the category Ic. Thyroid autoimmunity was significantly more prevalent among patients with documented recurrent miscarriages (66/44, 36%), compared with patients with no such data (4/18, 22%) (P<0.001). Among patients with history of recurrent miscarriages, ten patients (23%) had overt hypothyroidism, requiring levo-thyroxine replacement, while none of patients without previous miscarriages had any disorder of thyroid function.

Conclusion

Well-known association between autoimmune disorders, in the case of APS and thyroid autoimmunity, opens controversial issue of possibility of their synergistic, additive or potentiating effects on pregnancy complications as one of the classic manifestations of these relatively common syndromes.

DOI: 10.1530/endoabs.32.P598

P599

Inflammatory markers in polycystic ovarian syndrome and their association with cardiovascular risk factors

Sunil Kumar Kota1, Lalit Kumar Meher2, Sruti Jammula3 & Kirtikumar D Modi4

1Medwin Hospital, Hyderabad, Andhra Pradesh, India; 2MKCG Medical College, Berhampur, Orissa, India; 3Roland Institute of Pharmaceutical Sciences, Berhampur, Orissa, India.

Objectives

i) To determine and compare inflammatory markers including adiponectin, visfatin and IL-18 in patients with polycystic ovarian syndrome (PCOS). ii) To find out whether adiponectin and interleukin-18 (IL-18) is associated with markers of insulin resistance, hyperandrogenism and carotid intima-media wall thickness (CIMT) as a cardiovascular risk factor.

Methods

This is a prospective controlled study involving 60 consecutive euglycemic patients with PCOS (Rotterdam criteria) aged 50 years and body mass index (BMI) matched controls were included in the study. After detailed clinical evaluation including anthropometry, besides oral glucose tolerance test, fasting venous samples were analysed for IL-18, visfatin, adiponectin, highly sensitive C reactive protein (hsCRP) and complete lipid profile. We estimated body composition (total body fat and visceral adiposity index, VAT) by dual energy xray absorptiometry), CIMT (by Doppler ultrasonography), indices of insulin sensitivity (QUICKI) and resistance (homeostasis model assessment for insulin resistance, HOMA-IR) and free aneodor index (FAI). Data were analyzed using online graphpad quickcalce software and P<0.05 was considered statistically significant.

Results

PCOS patients had greater FAI (1.42 ±0.83 vs 0.64 ±0.4), higher HOMA-IR (2.13 ±0.05 vs 1.91 ±0.8) and lesser QUICKI (0.156 ±0.025 vs 0.163 ±0.015) than the control groups. Patients with PCOS have significantly increased serum IL-18 and visfatin levels than that of the control group (IL-18: 213.48 ±76.84 vs 170.42 ±41.11 gg/ml, visfatin: 73.35 ±11.54 vs 55.56 ±9.27 gg/ml, P<0.05) and hsCRP (2.56 ±0.64 vs 1.62 ±0.78 mg/l, P<0.004). Similarly, the PCOS group had significantly lower level of adiponectin (0.8 ±0.6 vs 1.04 ±0.49 ng/ml, P<0.001). Correlation coefficients of IL-18 were as follows: with CIMT (0.355), FAI (0.328), HOMA-IR (0.345) and waist circumference (0.367), each with P<0.05. Similarly, the correlation coefficients of adiponectin were with CIMT (−0.312), FAI (−0.343), HOMA-IR (−0.352) and waist circumference (−0.359), each with P<0.05.

Discussion

There arealteration of adipokines and other inflammatory markers in PCOS with increase in visceral, IL-18 and hsCRP and reduction in of adiponectin levels. Increased IL-18 and decreased adiponectin levels correlated with insulin resistance, obesity and hyperandrogenism.

Conclusion

These altered adipokine profile is associated with increased CVD risk in PCOS patients, leading to the suggestion that one of these markers like IL-18 can serve as potential therapeutic target in future for decreasing their CV risk.

DOI: 10.1530/endoabs.32.P599

P600

The effect of metformin on pregnancy outcome among filipino women with polycystic ovary syndrome

May Uyking-Naranjo, Evan Paulo Consencino, Roberto Mirasol & Joan Tan-Garcia

1St. Luke’s Medical Center, Quezon City, The Philippines.

Background

Polycystic ovary syndrome (PCOS) affects 5–10% of women in the reproductive age group. It is associated with insulin resistance and hyperinsulinaemia which is further aggravated during pregnancy. The use of metformin in PCOS is increasingly accepted but its therapeutic use during pregnancy is still a debatable
issue. There are few local studies on the use of metformin among PCOS patients and data are lacking among Filipinos.

Objectives
To determine the effect of metformin on maternal and neonatal outcome among pregnant Filipino women with PCOS.

Design
Cohort study

Setting: Review of outpatient medical records at a private infertility clinic

Population of interest: pregnant PCOS patients conceived with metformin


Results
Pregnant women who continued metformin during pregnancy had lower rate of first trimester spontaneous abortion (5 vs 36.2%, P < 0.001). A nonsignificant decrease in gestational diabetes was observed among PCOS women who continued metformin throughout pregnancy (19.0 vs 32.6%, P = 0.07). No pregnancy-induced hypertension was found between the two groups. There were no differences with regard to modes of delivery and gestational age of delivery (NSVD 44.6 vs 47.4%; CS 55.4 vs 52.6%, P = 0.07) (preterm 9.8 vs 27.2%; term 89.1 vs 97.3%; post-term 1.1 vs 0, P = 0.03). There were no differences in neonatal outcomes between the two groups that did not achieve statistical significance.

Conclusion
In women with PCOS, continuous use of metformin during pregnancy reduced the rate of first trimester spontaneous abortion.

DOI: 10.1530/endoabs.32.P600

P602
Relation of adiponectin and leptin to antropometric and metabolic parameters in women with polycystic ovaries syndrome

Tatjana Grgurović1, Jelena Nedeljkovic1, Tatjana Popovic1, Željka Mirković1, Ivana Miličević1, Svetozar Damjanovic1, Dusan Ilic1 & Svetozar Damjanovic1

1Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Belgrade, Serbia; 2Clinical-Hospital Center “Bežanijska kosa”, Belgrade, Serbia; 3Institute for Biologic Investigations “Sinisa Stankovic”, Belgrade, Serbia.

Introduction
Women with polycystic ovary syndrome (PCOS) are characterized with insulin resistance and hyperinsulinaemia. Adiponectin and leptin are adipose tissue-specific products and are correlated with insulin resistance. The aim of the study was to access the relation of adiponectin with anthropometric, metabolic and hormonal parameters in a group of women with PCOS.

Methods
We studied 57 non-obese women with PCOS diagnosed using ESHRE/ASRM criteria (PCOS: age 24.8 ± 5.6 years, BMI: 22.6 ± 3.8 kg/m²) and 22 BMI-matched healthy women (controls: age 27.8 ± 4.9 years, BMI: 21.8 ± 3.3 kg/m²). Whole body fat mass (WBFM) and abdominal fat mass (AFM) were determined by bioelectric impedance (Tanita). In all subjects serum concentrations of glucose, insulin, total cholesterol (TC), HDL, LDL, triglycerides, adiponectin, leptin, testosterone, and SHBG were determined. HOMA was calculated using standard formula.

Results
PCOS had more WBFM in comparison to controls (18.47 ± 7.68 kg vs 13.02 ± 5.83 kg, P = 0.004), while there was no difference in AFM between groups. AFM had higher testosterone (2.6 ± 1.0 vs 1.7 ± 1.6 mmol/l; P < 0.001) and lower SHBG (42.3 ± 26.1 vs 64.3 ± 29.9 nmol/l; P < 0.001). There were no differences between PCOS and controls in adiponectin (8.4 ± 3.5 vs 9.8 ± 3.8 µg/ml; P = 0.15), leptin (19.1 ± 17.9 vs 16.4 ± 16.1 µg/ml; P = 0.47), and HOMA index (3.5 ± 1.8 vs 3.2 ± 1.7; P = 0.76). There were no differences between groups in other measured parameters. Positive correlation in both groups was found between adiponectin and HDL (PCOS: r = 0.46, P < 0.001; controls: r = 0.53, P = 0.01), and leptin with WBFM (PCOS: r = 0.71, P < 0.001; controls: r = 0.68, P = 0.001), AFM (PCOS: r = 0.63, P < 0.001; controls: r = 0.73, P = 0.001) and HOMA (PCOS: r = 0.41, P < 0.002; controls: r = 0.52, P = 0.016). Leptin had negative correlation with SHBG only in PCOS group (r = -0.42, P = 0.001). Other measured parameters did not correlate with leptin and adiponectin in both groups.

Conclusion
We did not show difference in plasma adiponectin and leptin concentrations between our group of PCOS women and BMI matched healthy controls. Leptin showed better correlation with obesity and insulin resistance in comparison to adiponectin in both groups. Analyses on larger number of subjects for the relation of adipokines with metabolic indices in PCOS is needed.

DOI: 10.1530/endoabs.32.P602

P603
PON1-108 TT and PON1-192 RR genotypes are more frequently encountered in Greek PCOS than non-PCOS women, and are associated with hyperandrogenemia

George Mastorakos1, George Paltoglou1, George Tavernarakis2, Panagiotis Christopoulos1, Maria Gazouli1, Efthimios Deligeoroglou1 & George Creatsas1

1Professor of Endocrinology, University of Athens, Athens, Greece; 2Laboratory of Biology, University of Athens, School of Medicine University of Athens, Athens, Greece.

Objective
To investigate the frequencies of three paraoxonase (PON1) polymorphisms in Greek polycystic ovary syndrome (PCOS) and non-PCOS women, and their genotypes in association with hyperandrogenemia and insulin resistance.

Design
Case–control genetic association study.

Patients
PCOS cases (NH criteria) and 112 controls.

Main outcome measure
Genotyping of the c.108C>T (PON1-108), the c.163T>A (PON1-55) and the c.575A>G (PON1-192) polymorphisms and measurement of baseline androgen and insulin resistance profile.
Results
The PON1-108 TT and PON1-192 RR genotypes were more frequently encountered in the PCOS than in the control group. The PON1-192 R allele frequency was greater in the PCOS than in the control group. Comparing the PCOS and the control groups, statistical significances favored a recessive and a dominant genetic model, respectively, for the single PON1-108 T and PON1-192 R alleles. Free androgen index (FAI) levels were higher in patients with PON1-108 TT, while testosterone, FAI and dehydroepiandrosterone sulfate (DHEAS) levels were higher in patients with PON1-192 RR than in patients with the wild or the heterozygous genotype.

Conclusions
The decreased PON1 activity-associated PON1-108 TT and the PON1-192 RR genotypes are more frequently found in Greek PCOS women and are associated with hyperandrogenemia. Hyperandrogenemia must depend also on other genetic factors because the same genotypes were not associated with hyperandrogenemia in the control group. Through identification of the involved polymorphisms women with PCOS could potentially have a better therapeutic screening.

DOI: 10.1530/endoabs.32.P603

P604
C-reactive protein and gestational diabetes mellitus
Oksana Kononova1, Andrei Pirstrom1, Volha Vasilikova2 & Tatiana Mokhort1
1Gomel State Medical University, Gomel, Belarus; 2Belarusian Medical Academy of Post-Graduate Education, Minsk, Belarus; 3Belarusian State Medical University, Minsk, Belarus; 4Gomel State Medical University, Gomel, Belarus.

Aim
The aim of this study was to investigate the role of C-reactive protein (CRP) in gestational diabetes mellitus.

Material and methods
We studied 65 healthy pregnant women aged 29.75 ± 5.59 years. All women referred for a 100-g oral glucose tolerance test following an abnormal result on a screening. The demographic data, waist circumference, height, and weight of the participants were recorded. Fasting levels of insulin, triglycerides (TG), CRP, fasting blood glucose (FBG) and HbA1c were measured.

Results
Based on oral glucose tolerance testing, participants were divided into two groups: normal glucose tolerance (NGT) (n=17) and gestational diabetes mellitus (GDM) (n=48). The mean CRP level was highest in GDM group (9.67±5.37 mg/l), followed by NGT (2.56±1.73 mg/l), (P<0.0001). The mean FBG (4.98±0.51 vs 4.48±0.58 mmol/l, P<0.05), HOMA-IR (3.14±1.63 vs 1.83±0.62, P<0.05) and TG levels (1.95±0.65 vs 1.35±0.58 mmol/l, P<0.05) in the women with GDM were significantly higher than those in the NGT group.

CRP was positively correlated with first trimester pregnancy BMI (r=0.51, P<0.05), HOMA-IR (r=0.47, P<0.05), HbA1c (r=0.44, P<0.05), HOMA-IR (r=0.47, P<0.05) and FBG (r=0.41, P<0.01).

By multivariate logistic regression analysis, we showed elevated CRP levels to be independent risk factors for the development of hyperglycemia.

Conclusions
In women with GDM, there is evidence of increased CRP during the first trimester. The further evaluation will be needed to clarify this association.

DOI: 10.1530/endoabs.32.P604

P606
Concordance study of pathological results of fertility hormones
Miriam Menacho Roman1, Antonio Becerra Fernandez2, Gilberto Perez Lopez3, Rosa Villar Vicente3 & Jose Manuel del Rey Sanchez1
1Department of Biochemistry, Hospital Universitario Ramon y Cajal, Madrid, Spain; 2Gender Unit Department of Endocrinology, Hospital Universitario Ramon y Cajal, Madrid, Spain; 3Department of Endocrinology, Hospital Comarcal de Melilla, Melilla, Spain; 4Department of Endocrinology, Hospital Universitario de Fuenlabrada, Madrid, Spain.

Introduction
During a normal menstrual cycle, serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2), and progesterone (P4) can vary widely between cycles for the same woman, as well as between different women. Reliable reference values based on the local population are important for correct interpretation of laboratory results.

Aims
To evaluate the discrepancy of the results on fertility hormones by two different techniques.

Material and methods
We analyzed 130 patient samples processed: ci16200 ARCHITECT (Abbott) by chemiluminescent microparticle immunoassay (CMIA), and COBAS E-411 (Roche) by electrochemiluminescence immunoassay (ECLIA). We compared normal and pathological findings for women in follicular (FP), ovulatory (OP), luteal phase (LP), in menopause and in men, according to the normal ranges of each manufacturer. Discrepant pathological values are considered an increase/decrease in 5% of concordant results between two techniques.

Results
The results provided by COBAS increase E2 30%, FSH 17%, LH 39% and P4 just 4%. Reviewing the results of the assays performed is concluded that the pathological discrepancy for low cutoff (LC) and high cutoff (HC) are present: E2: LC: 17.3% in OP, 18% in LP, 9.5% in FP, 7.9% in menopause, HC: 11.8% in FP, 10.2% in LP, 20.5% in menopause. FSH: LC: 17.3% in OP, HC: 9.2% in LP. LH: HC: 6% in FP and 6% in menopause. HC: 8.5% in men and 6.1% in FP. P4: LC: 13.4% in men and FP. HC: 57% in men. 37% in FP, 5.9% in LP and 46% in menopause.

Conclusions
Normal values offered by manufacturers are very similar. The results obtained by COBAS are higher than ARCHITECT to E2, FSH and LH. There is discrepancy for P4 and E2 as there is an increase and/or decrease very marked pathological results depending on the demographic universe although slight discrepancy also exists for FSH and LH.

DOI: 10.1530/endoabs.32.P606
Introduction

Uric acid may increase cardiovascular risk, exerting proinflammatory, pro-oxidant and proliferative actions at the endothelial cell level. Classic and non-classic cardiovascular risk markers cluster in women with polycystic ovary syndrome (PCOS), uric acid being proposed as one of them. The studies available at present regarding serum uric acid levels in PCOS patients are scarce and controversial. The aim of the study was to examine the relationship between uric acid, obesity and insulin resistance in obese and non-obese patients with PCOS.

Methods

Thirty-eight overweight and obese women with PCOS and 30 controls matched for age and BMI were included in this study. Anthropometric variables, hormonal and metabolic profiles including measurements of uric acid and insulin levels were evaluated in both groups. Insulin resistance was quantified by homeostasis model assessment (HOMA).

Results

We did not find any statistically significant differences in uric acid levels between PCOS women and controls, but obese PCOS patients had significantly higher levels of uric acid compared to overweight women with PCOS. Obese patients with PCOS also had significantly higher levels of HOMA compared with overweight women with PCOS. In the control group, even the levels of uric acid was higher in obese compared to overweight women, the difference was not statistically significant. A significant positive correlation was found between uric acid levels and BMI, waist circumference, insulin levels and HOMA in PCOS group. Using stepwise linear regression analysis, only BMI which was responsible of 42.1% of the variability observed in serum uric acid concentrations, was retained by the regression model.

Conclusions

Our results suggest that obesity is the main determinant of plasma uric acid concentrations in PCOS patients. Insulin and HOMA are also involved in a lesser extent, but their role remain to be clarified in further studies.

DOI: 10.1530/endoabs.32.P608

P609

Prevalence of polycystic ovary syndrome in infertile patients in Albania

Mimoza Dollenga, Thanas Fureraj, Kosta Dhimia, Edmond Biziqi & Artan Simaku

1Health Centre No. 6, Tirana, Albania; 2University Hospital Centre ‘Mother Teresa’, Tirana, Albania; 3ANDC Clinic, Tirana, Albania; 4Institute of Public Health, Tirana, Albania.

Introduction

Polycystic ovary syndrome (PCOS) is the most common gynecological endocrinopathy. Women with PCOS are at increased risk of reproductive problems including infertility, endometrial cancer, late menopause and also metabolic aberrations, including insulin resistance, type 2 diabetes mellitus, dyslipidemia and cardiovascular diseases. There is very few data available on prevalence of PCOS on infertile population in Albania. The aim was to evaluate the prevalence of PCOS among infertile women according to Rotterdam criteria.

Methods

This is a cross sectional study which included 544 participants who presented to a infertility clinic in Tirana city from January 2010-December 2011. PCOS were diagnosed using universal assessment of ultrasonographic parameters, hormonal profiles and clinical histories. Women with other endocrinological disorders were excluded from the study.

Results

The mean age of study population was 30±8 years. 155 (28.5%) women had regular menstrual cycle and no sign of hirsutism or acne. One hundred and seventy-seven women (32.5%) had menstrual symptoms such as oligo-anovulation without hirsutism or acne. Thirty-eight (6.9%) manifested androgenic symptoms with regular menstrual cycle. The prevalence of PCOS was 38.7% (95% CI 34.6-42.9%).

Conclusion

Rotterdam criteria were effective for diagnosis of PCOS.

Keywords

PCOS, Rotterdam Criteria, hirsutism, infertility.

DOI: 10.1530/endoabs.32.P609

P610

Association of advanced glycosylation end products receptor polymorphisms with coronary heart disease in postmenopausal women

Xenofon Xyrafas, Konstantinos Toutouzas, Sarantis Livadas, Athanasios Karachalios, Christodoulos Stefanidis, Neoklis Georgopoulou & Evanthia Diamanti-Kandarakis

1Endocrine Unit, Third Dept. of Internal Medicine, Athens University Medical School, Athens, Greece; 2First Cardiology Clinic, School of Medicine, Athens University, Athens, Greece; 3Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, University of Patras Medical School, Patras, Greece

Background

Recent studies have suggested an important role of advanced glycosylation end products receptor (RAGE) in the development of atherosclerosis. However, investigation of the relationship between RAGE polymorphisms (−429T/C, −374T/A) and coronary heart disease (CHD) has shown contradictory results. Furthermore, hyperandrogenemia in women postmenopause has been associated with an adverse CHD risk profile.

Aim of the study

To investigate any possible relationship between RAGE polymorphisms with CHD and the association of RAGE polymorphisms with cardiovascular risk factors in postmenopausal women.

DOI: 10.1530/endoabs.32.P610
This case highlights the importance of endocrine assessment in the case of amenorrhea because of postoperative gonadotroph deficiency. By disappearance of pelvic pain. The postoperative ultrasound examination radiotherapy was indicated for the residual tissue. The evolution was marked within the pituitary, extending to the optic chiasm and to sphenoid and a second adenomas are more difficult to diagnose in women generally in perimenopausal or tumoral syndrome and endocrine profile of primary hypogonadism. Gonadotroph adenomas. These adenomas often arise in middle-aged men presenting with hyperandrogenemia and its role as a predisposing factor of atherosclerosis needs further evaluation.

Methods
Ninety-six menopausal women (28 diabetics – 68 non-diabetics, mean age: 68, 34 years) who underwent coronary angiography were genotyped for the −429TT/C and −374TA/variants of RAGE. In this group, androgen and estrogen levels, lipid parameters, glucose, HbA1c and insulin were determined and free androgen index was calculated.

Results
There was no significant difference in RAGE polymorphism frequencies between women with CHD confirmed in coronary angiography and those without CHD, although a cardioprotective trend was disclosed for 374AA polymorphism. Regarding hormonal/metabolic profile, women with homozygosity for the −429 allele (TT) had significantly lower levels of HDL (43.7 ± 17.16 vs 52.95 ± 14.47, P = 0.036) and SHBG (42.73 ± 18.17 vs 52.55 ± 20.71, P = 0.038) compared to heterozygotic subjects (TC) and significantly higher levels of triglycerides (151.75 ± 50.65 vs 125.89 ± 36.64, P = 0.042), FFA (1.85 ± 1.43 vs 1.17 ± 0.84, P = 0.042) and androstenedione (1.61 ± 1.01 vs 1.22 ± 0.58, P = 0.033). Women with homozygosity for the −374 allele (AA) had significantly lower LDL levels (83.8 ± 21.96 vs 105 ± 42.97, P = 0.046) compared to heterozygotic (AT) subjects.

Conclusion
Our data did not demonstrate an association between polymorphisms of the RAGE gene and CHD in menopausal women. However, homozygosity for the –429 allele (TT) of RAGE is associated with an adverse lipid profile and hyperandrogenemia as its role as a predisposing factor of atherosclerosis needs further evaluation.

DOI: 10.1530/endoabs.32.P610

P612
Menstrual function in women of reproductive age with acromegaly
Alessandra Prell1, Lidia Logotuta2, Yana Zaydieva2, Galina Stashuk1, Andrey Perfiliev3 & Irena Ilovayskaya1
1Moscow Research Clinical Institute, Moscow Region, Russia; 2Moscow Research Institute of Obstetrics and Gynecology, Moscow Region, Russia.

In purpose to characterize the disturbances of menstrual function in acromegalic women of reproductive age, we investigated 19 women with de novo acromegaly diagnosed at the age of 19–39 (median age 28) years. Before diagnosis, an average duration of acro-signs was 3.8 years, after diagnosis we observed women for 5 years. Among the first meaningful symptoms menstrual irregularities and/or infertility were noted in 13 (73.7%) cases. Initial levels of GH were 71 (31–135) mIU/l, IGF-1 775 (638–971) ng/ml, hyperprolactinemia was noticed in four (21%) cases. Macro/microadenomas were found in 17/2 (89.5/10.5%) cases. Most of the patients (n = 12, 63.2%) had hysterosurgery, afterwards eight of them started therapy with somatostatin analogues (SSA). Seven (36.8%) patients received only medical therapy (n = 5 SSA; n = 2 SSA + dopamine agonists). After treatment seven (36.8%) patients had controlled acromegaly (four after surgery, three on SSA), in other patients GH and IGF-1 levels were above target criteria. Menstrual disturbances were observed in four (21.1%) cases (persisted in two patients, and a hypogonadotrophic hypogonadism developed after surgical treatment in two women with initially normal menstrual cycle). In other women with initial menstrual dysfunction a restoration of the normal menstrual cycle was noted due to basal treatment of acromegaly. Three patients became pregnant during treatment with SSA (two with controlled acromegaly and one with partially controlled), one of them wished to terminate a pregnancy, two others did not stop the SSA therapy and gave birth in time to healthy babies.

Conclusions
Different menstrual cycle disorders coincided with the first symptoms of acromegaly in women of reproductive age. Algorithm of examination of women in reproductive age should include a minimum screening for acromegaly. We support the point of view that SSA therapy (in our study – Sandostatin LAR) is not harmful for a fetus and could be continued during pregnancy in women with acromegaly.

DOI: 10.1530/endoabs.32.P612

P613
Mechanisms of menstrual disorders in type1 diabetic women
Ines Kamoun1, Ikram Wassai2, Hajar Kandara, Faten Haj Kacem, Zinet Turki & Claude Ben Slama
Department of Endocrinology and Metabolism, National Institute of Nutrition, Tunis, Tunisia.

Introduction
Type 1 diabetic women have generally more menstrual disorders than healthy women.

Objectives
Identify the main mechanisms responsible of menstrual disorders in type1 diabetic women.

Patients and methods
We conducted a comparative transversal study including 70 patients with type 1 diabetes: Thirty-three having menstrual disorders (group M) and 37 with regular menstrual cycles (group N). We compared the clinical, metabolic and hormonal features of these two groups, in order to access a possible correlation between these parameters and menstrual disorders in these patients.

Results
Our study shows that patients who had a delayed menarche had a diabetes duration significantly longer than the other patients (P = 0.02).

On the other hand, our patients were overdosed in basal insulin and the dose of basal insulin was significantly higher in group M (0.78 IU/kg per day vs 0.61 IU/kg per day; P = 0.008).

Also, in group T, BMI was significantly lower in patients with 25–28 days dexamethasone compared to those who had 30–32 days dexamethasone (P = 0.02). Hormonal assays showed significant negative correlation between the total daily insulin dose and SHBG (P = 0.005).

Similarly, we found that the average testosterone level increased with the insulin dose, but without any significant correlation.

DOI: 10.1530/endoabs.32.P613
P614
Mitochondrial function of pregnant women with subclinical hypothyroidism and gestational hypertension
Anne-Dorthe Feldthuisen1,2, Jacob Larsen2, Palle Lyngsie Pedersen2,4, Tina Toft Kristensen1, Stine Anthonsen2 & Jan Kvetny1,2
1Department of Obstetrics and Gynaecology, Naestved Hospital, Region Zealand, Denmark; 2The Mitochondrial Research Unit, Naestved Hospital, Region Zealand, Denmark; 3Department of Clinical Pathology, Naestved Hospital, Region Zealand, Denmark; 4Department of Clinical Biochemistry, Naestved Hospital, Region Zealand, Denmark; 5Department of Otorhinolaryngology, Slagelse Hospital, Region Zealand, Denmark; 6Endocrinological Clinic, Department of Internal Medicine, University of Southern Denmark, Naestved Hospital, Region Zealand, Denmark.

Introduction
Subclinical hypothyroidism (subhypo) is linked to gestational hypertension (gestHT) and preeclampsia. Thyroid hormones have major influence on mitochondrial activity and the mitochondrial membrane potential (MMP) reflects the functional status of the mitochondria.

Aim
The aim was to estimate whether mitochondrial function is impaired in pregnant women with or without gestHT.

Methods
We included third trimester pregnant women consulting the department of obstetrics. The cases had subhypo (raised concentrations of TSH and normal concentrations of thyroid hormones). The second group were healthy pregnant women. The third group represented healthy non-pregnant women as controls. None of the women had any thyroid disease or medication. A blood sample was drawn to measure TSH and thyroid hormone. The mitochondrial function of stained mononuclear blood cells were measured by flow cytometry. GestHT was defined as blood pressure >140/90 mmHg.

Results
We present preliminary results of 102 patients and 40 controls. The prevalence of subhypo among pregnant women was 17%. The MMP was increased among pregnant women vs controls (P=0.03) and MMP was further increased among pregnant women having gestHT (P=0.01), an increase which was absent in pregnant women with gestHT and subhypo. Reactive oxygen species (ROS) was increased in pregnant women vs controls (P=0.006) but we found no differences in ROS between healthy pregnant women and women having gestHT. We have not yet examined the subgroup with subhypo.

Conclusion
The 17% prevalence of subhypo in pregnant women is higher than the commonly cited prevalence of 2-3%. The MMP of pregnant women was increased compared to non-pregnant women and further increased when gestHT was present. We suggest a possible physiological adaptation, which was absent in subhypo. This observation of an impaired mitochondrial function in subhypo may elucidate the higher frequency of complications like gestHT and preeclampsia in pregnant women with subhypo.

DOI: 10.1530/endoabs.32.P614

P615
Hormonal disorders and breast diseases in adolescent girls
Olga Gumeniuk, Yuriy Chernenkov, Nataliya Zakharova, Irina Ivanenko, Svetlana Kunina & Anna Kunina
Saratov State Medical University, Saratov, Russia.

Introduction
The breast is a hormone-dependent organ.

Purpose
To study hormonal disorders peculiarities and breast diseases in adolescent girls.

Patients and methods
Examined were 867 adolescent girls (aged 12–18), including 154 girls with breast diseases and dysmorphogenies (macromastria, hypoplasia, striae). The examination, total clinical examination, hormonal analysis and ultrasound examination were conducted. Data are expressed as median.

Conclusion
The overdose of basal insulin may explain a large part of the menstrual disorders in type 1 diabetes. Obesity can worsen the situation and increase the menses duration.

DOI: 10.1530/endoabs.32.P615

P616
Menstrual cycle length is associated with metabolic syndrome in young Korean women with oligomenorrhea
Jee-Young Oh, Yeon-Ah Sung & Hye Jin Lee
Ewha Womans University School of Medicine, Seoul, Republic of Korea.

Introduction
Although menstrual irregularity, including oligomenorrhea (OM), is associated with insulin resistance and hyperandrogenism, the relationship between the severity of menstrual infrequency and clinical phenotypes in young women with OM is unclear. We evaluated whether a longer menstrual cycle length is associated with less favorable metabolic features in young women.

Methods/design
A total of 1296 young women (aged 15–39 years old) with a menstrual cycle length of greater than 40 days and 1634 regular cycling women voluntarily participated. Metabolic parameters, insulin sensitivity index, and testosterone levels were measured. Oligomenorrheic women were divided into two groups: i) severe OM (menstrual cycle length >60 days) and ii) mild OM (menstrual cycle length 40–60 days).

Results
Women with severe OM displayed higher levels of most metabolic parameters and higher testosterone levels compared to women with mild OM. Among obese subjects (BMI ≥25 kg/m²), women with severe OM had significantly higher levels of systolic blood pressure, insulin, cholesterol, and testosterone and lower insulin sensitivity indices compared to women with mild OM (even if they had similar BMI and waist circumference). Non-obese subjects displayed the same results. Severe OM was associated with metabolic syndrome (odds ratio 2.2, 95% CI 1.2–4.0) after adjustment for age, BMI, family history of diabetes, insulin sensitivity index, and free testosterone levels.

Conclusion
Oligomenorrheic women with a menstrual cycle length of greater than 60 days should be more closely monitored for metabolic syndrome than women with a menstrual cycle length 40–60 days.

DOI: 10.1530/endoabs.32.P616

P617
Obstructive sleep apnea in Bulgarian patients with polycystic ovarian syndrome
Antoaneta Gateva1,2, Zdravko Kamenov1,2, Tsanko Mondeshki1,3, Radoslav Bilyukov1,3 & Ognian Georgiev1,3
1Medical university Sofia, Sofia, Bulgaria, 2University Hospital Alexandrovska, Clinic of endocrinology, Sofia, Bulgaria, 3University Hospital Alexandrovska, Clinic of pulmonology, Sofia, Bulgaria.

Introduction
OSA is a rare condition in premenopausal women that do not have PCOS and is most frequently associated with obesity. On the other hand the risk in PCOS

Endocrine Abstracts (2013) Vol 32
patients is thought to be significantly higher. The aim of the study was to investigate the prevalence of sleep apnea in Bulgarian patients with PCOS and/or obesity.

Methods
The study included 30 women – 11 obese, 13 nonobese PCOS and six obese PCOS patients. Anthropometric measurements, biochemical and hormonal assessment were performed for every patient. Polysomnography was carried out according to standard laboratory protocol.

Results
In nonobese patients with PCOS there were no detected cases of sleep apnea. In obese women without PCOS OSA was found in 54.5% and in obese PCOS in 33.3%. There was a strong positive correlation between the age of the patient and the number of obstructive apneas and hypopneas per hour, apnea/hypopnea index and respiratory disturbance index (r = 0.63, r = 0.55, r = 0.68 and r = 0.69 respectively). An even stronger correlation was observed between BMI and the abovementioned indices (r = 0.72, r = 0.54, r = 0.82 and r = 0.81 respectively).

Patients with and without OSA differed significantly in the presence of visceral obesity according to waist-to-hip ratio and waist-to-stature ratio, the rate of metabolic syndrome, fasting IRI and HOMA-index. There was no difference in testosterone levels between patients with and without OSA.

Conclusion
Nonobese PCOS patients do not have higher prevalence of OSA. The main factors for OSA presence are age and obesity and not the PCOS status.

DO: 10.1530/endoabs.32.P617

P618
Plasma kisspeptin levels in polycystic ovary syndrome

Emrah Yerlikaya1, Fulya Akın1, Sebahat Turgut2, Guzin Yaylali1, Senay Topsakal1, Ceylan Ayada2 & Celile Hatipoglu3

1Department of Endocrinology, Pamukkale University, Denizli, Turkey; 2Department of Physiology, Pamukkale University, Denizli, Turkey; 3Department of Public Health, Pamukkale University, Denizli, Turkey.

Introduction
Kisspeptin is a 54-amino acid peptide, which comprise a diverse group of peptides with many different functions related to energy metabolism and reproduction, pubertal development. It activates GPR54 receptor. Subcutaneous administration of kisspeptin-54 to women with regular menstrual cycles results in an increase in LH and FSH. All these findings show that the GPR54 system may play a role in the function of the hypothalamic–pituitary–gonadal axis. PCOS is characterized by hyperandrogenism and chronic anovulation. Frequently increased LH levels accompany to PCOS. Based on these findings, we designed this study to further characterize metastin levels in women with PCOS and controls.

Methods
Women with PCOS and 28 healthy women, recruited from the Endocrinology Clinic of Pamukkale University, were studied. The diagnosis of PCOS was based on the revised criteria of Rotterdam. Anthropometric measurements were performed. A fasting blood sample was obtained in the morning for measurement of glucose, insulin, PRL, LH, FSH, estradiol, total testosterone, sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulphate (DHEA-S), 17-hydroxyprogesterone and TSH. Free androgen index and HOMA-IR values were calculated. Kisspeptin levels were also measured with an ELISA kit.

Results
We searched the relationship between metastin and degree of obesity and insulin resistance. Twenty-six PCOS woman were overweight/obese, the remaining 14 were normal weight. In our study, obese/overweight PCOS woman were more insulin resistant than non-obese. We found no correlation between the kisspeptin and body mass index, HOMA-IR values.

Conclusion
There are no such studies looking this relationship in the literature. In the literature, plasma kisspeptin levels were found lower in obese and insulin-resistant PCOS. This inaccordant result may be due to small sample size or sex steroid effects on kisspeptin levels.

DO: 10.1530/endoabs.32.P619

P620
Potential discriminant factors for different pcos phenotypes

Mirjana Stojkovic, Biljana Beleslin, Jasmina Cirić, Slavica Savic, Tanja Nisic, Milos Stojanovic, Tijana Lalic, Bozo Trbojevic & Milos Zarkovic

Clinic of endocrinology, diabetes and metabolic diseases Clinical Center of Serbia, Belgrade, Serbia.

Background
Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age. It is a heterogeneous disorder characterized by oligo- or anovulation (ANOV), biochemical or clinical manifestations of hyperandrogenemia (HA) and polycystic ovaries (PCO). Combination of these three characteristics makes four phenotypes of PCOS: phenotype 1 (ANOV + HA + PCO), phenotype 2 (ANOV + HA), phenotype 3 (HA + PCO) and phenotype 4 (ANOV + PCO). The differences between these four phenotypes are still undefined and the subjects of study.

Methods
We evaluate 92 PCOS women using stepwise linear discriminant analysis with combination of these three characteristics makes four phenotypes of PCOS: phenotype 1 (ANOV + HA + PCO), phenotype 2 (ANOV + HA), phenotype 3 (HA + PCO) and phenotype 4 (ANOV + PCO). The differences between these four phenotypes are still undefined and the subjects of study.

Results
We evaluate 92 PCOS women using stepwise linear discriminant analysis with combination of these three characteristics makes four phenotypes of PCOS: phenotype 1 (ANOV + HA + PCO), phenotype 2 (ANOV + HA), phenotype 3 (HA + PCO) and phenotype 4 (ANOV + PCO). The differences between these four phenotypes are still undefined and the subjects of study.

Conclusion
Some studies showed increased levels of kisspeptin in PCOS. Our study did not support these findings. This may be result of the obesity and insulin resistance that may have negative impact on kisspeptin levels. Leptin deficiency or resistance may be an explanation for a linkage between obesity, insulin resistance and PCOS.

DO: 10.1530/endoabs.32.P618

P619
Relation of plasma kisspeptin levels with obesity and insulin resistance in polycystic ovary syndrome

Emrah Yerlikaya1, Fulya Akın1, Sebahat Turgut2, Guzin Yaylali1, Senay Topsakal1, Ceylan Ayada2 & Celile Hatipoglu3

1Department of Endocrinology, Pamukkale University, Denizli, Turkey; 2Department of Physiology, Pamukkale University, Denizli, Turkey; 3Department of Public Health, Pamukkale University, Denizli, Turkey.

Introduction
Majority of polycystic ovary syndrome (PCOS) women are anovulatory, overweight/obese and insulin resistant. Kisspeptins are the endogenous ligands for GPR54 highly expressed in pancreas. Some studies showed that kisspeptins may play in the regulation of islet function and they stimulate insulin secretion from mouse and human islets. Adipose tissue acts as an endocrine organ and its function may be regulated by kisspeptins. We designed this study based on that obesity, insulin resistance and reproductive function changes may be a reflection of the disruptions in kiss system.

Methods
Forty women with PCOS recruited from the Endocrinology Clinic of Pamukkale University were studied. The diagnosis of PCOS was based on the revised criteria of the European Society of Human Reproduction an Embryology American Society for Reproductive Medicine in 2003. Anthropometric measurements were performed. A fasting blood sample was obtained in the morning for measurement of glucose, insulin, PRL, LH, FSH, estradiol, total testosterone(T), sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulphate (DHEA-S), 17-hydroxyprogesterone and TSH. Free androgen index and HOMA-IR values were calculated. Kisspeptin levels were also measured with an ELISA kit.

Results
Women with PCOS had higher FAI, FG scores and DHEA-S levels, compared to controls. BMI, HOMA-IR values, fasting plasma glucose levels were higher in the PCOS group than in the control group. There was not statistically significant difference between the groups in terms of kisspeptin and LH:FSH ratios. We evaluated 92 PCOS women using stepwise linear discriminant analysis with combination of these three characteristics makes four phenotypes of PCOS: phenotype 1 (ANOV + HA + PCO), phenotype 2 (ANOV + HA), phenotype 3 (HA + PCO) and phenotype 4 (ANOV + PCO). The differences between these four phenotypes are still undefined and the subjects of study.

Conclusion
Some studies showed increased levels of kisspeptin in PCOS. Our study did not support these findings. This may be result of the obesity and insulin resistance that may have negative impact on kisspeptin levels. Leptin deficiency or resistance may be an explanation for a linkage between obesity, insulin resistance and PCOS.

DO: 10.1530/endoabs.32.P618

<table>
<thead>
<tr>
<th></th>
<th>BMI (kg/m²)</th>
<th>LH (IU/L)</th>
<th>HOMA-IR</th>
<th>HOMA-B</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANOV</td>
<td>27.1 ± 6.0</td>
<td>7.33 ± 4.69</td>
<td>1.49 ± 0.34</td>
<td>371.8 ± 391.7</td>
</tr>
<tr>
<td>PCO+HA</td>
<td>29.2 ± 8.0</td>
<td>5.30 ± 3.81</td>
<td>1.32 ± 0.39</td>
<td>423 ± 213.1</td>
</tr>
<tr>
<td>ANOV+HA</td>
<td>22.8 ± 4.4</td>
<td>11.13 ± 6.13</td>
<td>1.18 ± 0.28</td>
<td>535 ± 165.5</td>
</tr>
<tr>
<td>PCO+HA</td>
<td>24.9 ± 5.8</td>
<td>4.12 ± 2.62</td>
<td>1.40 ± 0.49</td>
<td>755.6 ± 1436.2</td>
</tr>
</tbody>
</table>
Conclusions
We concluded that LH, BMI, HOMA-IR and HOMA-B could be useful as discriminant factors in different PCOS phenotypes.
DOI: 10.1530/endoabs.32.P620

Growth hormone IGF axis – basic
P621
Delay stature and shox gene molecular abnormalities: about 4 families
Nora Soumeya Fedala1, Ali El Mehdi Haddam2, Farida Chentli1, Meriem Haddad1 & Lynda Akkache1
1Endocrinology, BAB El Oued Hospital, Alger, Algeria; 2Endocrinology, Bologhine Hospital, Alger, Algeria.

Introduction
These last years have seen emerge identification of a large number of genes responsible of bone disease. La dyschondrosteosis: Leri weill is more important to know. It include short stature due to moderate micromelia mesomelic associated with a very characteristic deformity of the wrist: the Madelung deformity. This pathology is caused by haploinsufficiency of the SHOX gene, a gene essential in regulating the growth and remodeling of skeletal. We report observations about two young patients AD and SM six and height years old who consulted for delay stature. They had mesomelic dwarfism and Madelung deformity. Hormonal balance was unremarkable. Radiography helped diagnose LERI WEILL syndrome. The family survey has identified several cases in the two families. The genetic study is underway.

Discussion and conclusion
Located in the pseudo autosomal region of the Xchromosomia PAR1, several molecular abnormalities can effect the shox gene. It may be mutation, deletion or duplication. Others conditions of growth are associated with SHOX: The LANGER dwarfism, Turner syndrome and even some cases called idiopathic growth retardation. These conditions must be recognized early to allow effective management of affected children and their families.

DOI: 10.1530/endoabs.32.P621

P622
A comparison of the in vitro production of IGFs, IGFBP-4 and PAPP-A in cultures of visceral and subcutaneous adipose tissue fragments from obese subjects
Jan Frystyk1, Mette Faurholdt Gude1, Rikke Hjortebjerg, Claus Oxvig2 & Steen Bonløkke Pedersen3
1Medical Research Laboratory, Department of Clinical Medicine, Faculty of Health, Aarhus University, Aarhus, Denmark; 2Department of Molecular Biology and Genetics, Faculty of Science and Technology, Aarhus University, Aarhus, Denmark; 3Department of Endocrinology and Internal Medicine, Tage Hansens-Gade, Aarhus University Hospital, Aarhus, Denmark.

Background
Visceral adipose tissue (VAT) is less insulin sensitive and more harmful than subcutaneous adipose tissue (SAT). In adipocytes, IGF1 receptor signaling has been linked to insulin resistance, but it is unknown whether VAT and SAT also differ in production of IGFs. Therefore, we compared IGFs, IGFBP-4 and PAPP-A production in cultured fragments of VAT and SAT from obese subjects.

Methods
VAT and SAT was collected perioperatively during elective bariatric surgery from 17 women and 9 men (mean ± S.E.M.: age 38.7 ± 1.9 years, BMI 39.8 ± 0.9 kg/m²). Culture media collected after 48 h of incubation (500 mg tissue fragments) without (baseline) and with GH (100 µg/kg) were compared for concentrations of IGFs, IGFBP-4, PAPP-A and bioactive IGF1 as measured by IGF1 receptor bioassay.

Results
VAT and SAT produced similar amounts of IGF1 at baseline (mean and interquartiles: 0.25 (0.05–0.56) vs 0.06 (0.05–0.23) µg/l), but VAT produced more IGF1 than SAT after GH stimulation (0.58 (0.12–1.63) vs 0.30 (0.08–0.59) µg/l, P<0.05). IGF2 production was markedly higher in VAT than SAT (2.66 (1.47–3.84) vs 1.65 (1.09–2.21) µg/l, P<0.05), and in both compartments, baseline IGF2 production exceeded that of IGF1 (P<0.0001). VAT produced fourfold more PAPP-A than SAT (5.16 (4.20–7.00) vs 1.16 (0.96–1.56) µg/l, P<0.05). VAT also produced more IGFBP-4 (45.7 (24.5–69.3) vs 22.7 (18.2–37.7) µg/l, P<0.05). In accordance with these observations, levels of bioactive IGF1 were higher in media from VAT than SAT at baseline (0.13 (0.03–0.19) vs 0.06 (0.05–0.10), P<0.05) as well as after GH stimulation (0.22 (0.10–0.37) vs 0.11 (0.05–0.18) µg/l, P<0.05).

Conclusion
VAT produced markedly more IGF2, PAPP-A and IGFBP-4 than SAT, resulting in a higher media IGF1 bioactivity. Furthermore, VAT was more sensitive to GH than SAT. Our data suggest that PAPP-A may control IGF-action in adipose tissue, in particular in VAT. This mechanism may have effects on local insulin sensitivity.

DOI: 10.1530/endoabs.32.P622

P624
Association between a common GH receptor polymorphism (exon 3-deletion), pre- and postnatal growth, serum insulin-like growth factor 1 and reproductive function in 838 healthy young males
Mikkel Andreassen, Rikke Beck Jensen, Niels Jørgensen & Anders Juul
Rigshospitalet, University of Copenhagen, Copenhagen, Denmark.

Introduction
A common genetic polymorphism in the GH receptor (GHR) is deletion of the entire exon 3 sequence (GHRd3 isofrom). The GHRd3 isofrom seems to be more sensitive with increased downstream GH signalling in activated exon 3 deleted receptor dimers (GHRd3/d3) compared to full length receptor dimers (GHRR8). Presence of the GHRd3 isofrom might be associated to pre- and postnatal growth and pubertal development in boys, although controversy exists. The aim was to investigate the influence of exon 3 GHR polymorphism on pre- and postnatal growth, insulin-like growth factor 1 (IGFI) serum levels, IGF binding protein 3 (IGFBP-3) levels, reproductive hormone levels (gonadotropins, testosterone, estradiol, sex hormone binding globulin) and semen quality (semen volume, sperm counts, sperm motility and sperm morphology).

Endocrine Abstracts (2013) Vol 32

15th European Congress of Endocrinology 2013
P625
SNPs within the GH signaling pathway are associated with the fast, but not the long term, IGF1 response to GH replacement therapy in GH deficient adults
Camilla Glad1,2, Edna de Jesus Litenski Barbosa1, Helena Filipsson Nyström1, Lena Carlsson Ekander2, Staffan Nilsson4, Anna Nilsson1, Per Arne Svensson2 & Guidmundur Johannsson1
1Department of Endocrinology, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; 2Department of Molecular and Clinical Medicine, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; 3Service de Endocrinologia e Metabologia do Hospital de Clínicas da Universidade Federal do Paraná, Curitiba, Brazil; 4Department of Mathematical Statistics, Chalmers University of Technology, Gothenburg, Sweden.

Introduction
GH deficiency (GHD) in adults is associated with low serum levels of insulin-like growth factor 1 (IGF1) and a deteriorated cardio-metabolic profile. GH signaling pathway may be of functional relevance to the fast response to GHRT in GHD adults. In addition, these results highlight the fact that genetic factors are more likely to impact on the fast response to RT, when factors such as individual dose titrations, diet and life style choices etc. are less likely to influence the response marker.

Aim
The aim of this study was to test the hypothesis that single-nucleotide polymorphisms (SNPs) in genes within the GH signaling pathway impact on the fast (1 week) and/or long term (6 months and 1 year) IGF1 response to GHRT.

Patients and methods
Three hundred and thirteen consecutive GHD subjects (58.1% men; mean age 49.7 years) were studied before and after 1 week, 6 months and 1 year of GHRT. Response was defined as the percentage of change in IGF1 levels from baseline (fast response) and from 1 week (long term response). Six SNPs in the GHR, JAK2, STAT3b, SOCS2 and PIK3CB genes were selected for genotyping.

Results
Average genotyping success rate was 98.8%. In linear regression analyses adjusting for sex, age, and the GH dose, SNPs rs6873545 (GHR) and rs361072 (PIK3CB) were significantly associated with the percentage of change in IGF1 levels at 1 week of GHRT (P=0.031 and P=0.017 respectively). No SNP was significantly associated with the long term response.

Conclusion
Our results indicate that common genetic variants in genes with function in the GH signaling pathway may be of functional relevance to the fast response to GHRT in GHD adults. In addition, these results highlight the fact that genetic factors are more likely to impact on the fast response to RT, when factors such as individual dose titrations, diet and lifestyle choices etc. are less likely to influence the response marker.

DOI: 10.1530/endoabs.32.P625

Endocrine Abstracts (2013) Vol 32
**P628**

Sheehan’s syndrome females have a high incidence of cardiovascular morbidity and an increased prevalence of cardiovascular risk factors Ines Slim1, Nadra Bhouri1, Houneida Zaghouane2, Molka Chadli1, Monica Zoaouali1, Koussay Ach1, Amel Maaraoui1, Maha Kacem1, Chakib Kraiem1 & Larbi Chaieb2

1Department of Diabetes and Endocrinology, Farhat Hahed University Hospital, Sousse, Tunisia; 2Department of Physiology, Ibn Jazzar Faculty of Medicine, University of Sousse, Sousse, Tunisia. Department of Radiology, Farhat Hached University Hospital, Sousse, Tunisia.

**Introduction**

While severe GH deficiency (GHD) is a well-established feature of Sheehan’s syndrome (SS), the effects of GH deficiency in these patients has not been extensively investigated. In the present study we evaluated the cardiovascular risk in patients with SS.

**Methods**

Twenty female with SS and well-treated with cortisone and thyroid hormones was included. Metabolic syndrome according to IDF-2009 criteria and insulin resistance estimated by HOMA-IR were investigated. GHD was searched based on Glucagon test. Common carotid intima-media thickness (IMT) was measured by B mode ultrasound. Cardiovascular risk was assessed by SCORE.

**Results**

The GHD was found in 95% of patients. Hypertension represents the most frequent history of cardiovascular disease. The mean BMI was at 28.10 ± 6 kg/m², 35% of patients were obese. The mean waist circumference was at 99.3 ± 15 cm. Fasting glucose more than 5.5 mmol/l was present in 45% of subjects. A total cholesterol > 5.2 mmol/l was observed in 65% of cases, an LDL-C > 4.1 mmol/l in 35% of cases, and an HDL-C < 1.0 mmol/l in 15% and a triglyceride level >1.7 mmol/l in 60% of cases. Metabolic syndrome was present in 55% of cases. Forty percent of patients had insulin resistance. The IMT was not increased in all cases; the presence of atheromatous plaques was noted in one case. The IMT was positively correlated with diastolic blood pressure and LDL-C. Cardiovascular risk was moderate in 40% of cases and very high in 15% of cases. Patients with high cardiovascular risk had higher systolic blood pressure and fasting glucose.

**Conclusion**

These findings highlight the importance of closely cardiovascular and metabolic monitoring of patients with SS unsubstituted in GH and raise the question of the benefit of GH replacement in these patients.

**DOI:** 10.1530/endoabs.32.P628

---

**P629**

Determinants of carotid intima media thickness in acromegaly patients Merve Yilmaz1, Arzu Gedik2, Can Basaloglu2, Dilek Cinirim1, Hülya Ellidokuz2, Mustafa Secil1 & Abdurrahman Çomlekci1

1Endocrinology Department, Medical Faculty, Dokuz Eylul University, Izmir, Turkey; 2Radiology Department, Medical Faculty, Dokuz Eylül University, Izmir, Turkey; 3Biochemistry Department, Medical Faculty, Dokuz Eylul University, Izmir, Turkey; 4Biostatistics Department, Medical Faculty, Dokuz Eylul University, Izmir, Turkey.

**Introduction**

Acromegaly is a rare disease characterized by GH and IGF1 hypersecretion and increased cardiovascular mortality. Ultrasonographic measurement of carotid intima media thickness (CIMT) gives substantial information about early atherosclerosis. We aimed to evaluate CIMT and its determinants in a group of acromegaly patient.

**Patients and methods**

Forty-four acromegaly patient and 43 age, sex and body mass index (BMI) matched healthy controls were included. Blood pressure (BP), BMI, waist-to-hip ratio (WHR) measurements; plasma CRP, fibrinogen, lipid, fasting plasma glucose, GH, IGF1, insulin tests; HOMA-IR calculations and CIMT measurements were done.

**Results**

Right (P=0.017) and left (P=0.025) CIMT were found to be significantly higher in acromegaly group than the healthy controls. Right CIMT correlated positively with age, WHR and CRP; negatively with GH and IGF1. Besides, left CIMT showed positive correlation with age, diastolic BP, WHR, LDL-C and negative with IGF1. The linear regression analysis demonstrated that white age and CRP was the major determinants of right CIMT, only the age was so for the left CIMT. Both right (P=0.001) and left (P=0.020) CIMT were significantly different among active acromegaly (AA), cured acromegaly (CA) and healthy control groups. Right CIMT was significantly higher in CA group than the AA group and healthy controls and left CIMT was significantly higher in CA group than the healthy controls. The higher mean of age in the CA group is thought to be a possible explanation for the increased CIMT in the CA group.

**Conclusion**

Studies evaluating CIMT in acromegaly patients have depicted different results so far. In this study, we found increased CIMT in acromegics. Increased CIMT seems to be solely related to the age of the patient in parallel to previous reports. The disease activity and the other cardiovascular markers like glucose, lipids, BP are not found as confounding factors to increased CIMT.

**DOI:** 10.1530/endoabs.32.P629

---

**P631**

**GH therapy in Turner syndrome: growth rate indirectly correlated with age of therapy initiation**

Ioana Hristov1, Ramona Elena Axinte1, Cristina Prada1,2, Maria Cristina Ungureanu1,2 & Voichita Mogos1,2

1St Spiridon Hospital, Iasi, Romania; 2University of Medicine and Pharmacy: ‘Gr.T.Popa’, Iasi, Romania.

**Introduction**

Short stature is the most common physical abnormality in Turner syndrome (TS), with adult stature averaging 20 cm shorter compared to the general population. Aim To study the efficiency of early initiation for GH therapy on final stature for patients with Turner syndrome and to prove it’s important role in obtaining optimal growth rates.

**Results**

As of October 2012, 297 patients were enrolled in the study: 116 had received previous GH treatment. Mean (s.d.) age and body mass index of enrolled patients was 50.7 (15.4) years and 29.9 (6.8) kg/m² respectively. One hundred and fifteen adverse event (AEs) have been reported to date in 49 patients, with seven (in four patients) regarded as serious. Nine AEs in five patients were suspected as drug-related, with headache the most common (n = 3). Eight patients have so far discontinued treatment (four were GHD-naïve at study entry, four had received prior rhGH treatment). Of the eight patients who have discontinued, only one did so due to an AE.

**Conclusions**

Based on these interim results, Omnitrope treatment in adults with GHD is well tolerated in a real-life clinical practice setting; both in previously rhGH-naïve and previously treated patients. The ongoing PATRO Adults study will provide important data on the diabetogenic potential and overall safety of long-term GH replacement therapy in this population.

**DOI:** 10.1530/endoabs.32.P631
Glucose metabolism abnormalities in a population of acromegalic patients
Cátiadia Nogueira,1,2 Sandra Belo,1,2 Eduardo Vinha1, Ângela Magalhães1,2 & Davide Carvalho1,2
1Centro Hospitalar São João, Porto, Portugal; 2Faculty of Medicine, University of Porto, Porto, Portugal.

Discussion
In patients group of 15–20 years, we obtained the lowest growth rates, the
incriminated factor being the associated substitutive oestrogen therapy and it’s
effects on the bone plate.

DOI: 10.1530/endoabs.32.P631

P633 Evaluation of LIAISON XL vs IMMULITE 2000 IGF1
Mira Manor & Yizhak Mayer
Clalit Health Care, Tel Aviv, Israel.

Introduction
Insulin-like growth factor 1 is a single-chain polypeptide of 70 amino acids. Quantitative determination of IGF1 is a one-step sandwich chemiluminescence immunoassay (CLIA). IGF1 is being used by physicians as a screening test for GH deficiency and excess. It became crucial to find an alternative automated platform for the current available methods.

Design
Evaluation took place in an HMO central lab, currently using the SIEMENS IMMULITE 2000. Seventy-nine randomly outpatients serum samples collected from Clalit Central Laboratory. Fifty-three routine samples were tested on pre-modified IMMULITE kit, delivered from Screening Department Institute of Mother and Child, Warsaw Poland. Patients, controls and NEQAS samples were tested by: DiaSorin LIAISON IGF1, IMMULITE IGF1. Results were analysed according to patients’ age and gender.

Results
Correlation between LIAISON IGF1 and IMMULITE IGF1 was analysed for:
A. samples from Clalit central laboratory. B. samples delivered from abroad, pre-modified IMMULITE vs LIAISON. C. Samples delivered from abroad, new modified IMMULITE vs LIAISON. D. Samples delivered from abroad, new modified IMMULITE vs pre-modified IMMULITE. The r values were 0.9750, 0.9849, 0.9750, 0.9758, 0.9770, 0.9453 and 0.9729 respectively.

Conclusions
High correlation was observed between LIAISON and IMMULITE IGF1 together with high clinical agreement. It is concluded that the LIAISON IGF1 can be used as reliable and accurate kit for high throughput laboratories.

DOI: 10.1530/endoabs.32.P633

P634 GH therapy: never say never; clinical case
Irina Ghita, Corina Profiri, Georgetiana Constantinescu, Roxana Novac & Voicuha Mogoș
Department of Endocrinology, University of Medicine and Pharmacy ‘Gr. T. Popa’, Iasi, Romania.

We present the case of a patient diagnosed with panhypopituitarism at an adult age. The tenth child of a poor family, PA consulted the endocrinologist accompanied by his 65 year old mother. PA was 20 years old at the first consultation. He was, however, entrapped in the body of a 12 year old child, being only 139 cm tall and having no signs of puberty onset. He was slightly eunuchoid, with long limbs, due to delayed puberty, with microgenis and lack of androgen dependent hair, but otherwise harmoniously developed. He had low blood pressure and hypoglycemia. His skin was pale, dry and slightly carotene and infiltrated and his scalp and eyebrow hair was scarce. His clinical appearance was very suggestive for panhypopituitarism. Clinical supposition was confirmed by hormonal investigation: a low IGF1 (38 ng/ml, normal 250–600 ng/ml) and low basal GH (0.1 ng/ml, normal > 10 ng/ml), which didn’t increase at effort, insulin or clonidine tests, demonstrating a GH deficiency. TSH and T4 were below the normal limit, basal morning cortisol was low (5 µg/dl) and it maintained low values even after insulin stimulation. The tests revealed also a gonadotrope deficiency, with prepubertal LH, FSH and testosterone. MRI investigation showed partial empty sella, ectopic neurohypophysis and hypoplastic pituitary stalk (described midline effect accompanying GH deficiency in children). After 3 years of treatment with recombinant GH, thyroid hormones and glucocorticoids, the patient gained 20 cm in height, the clinical aspect improved, as well as the paraclinical values. At the moment, he also undergoes injectable testosterone treatment thereby growing five extra centimeters (final stature 174 cm) and developing secondary sexual characteristics. This case pleads in favor of GH therapy in panhypopituitary patients irrespective of the age of diagnosis with potential beneficial effects on growth.

DOI: 10.1530/endoabs.32.P634
Silver–Russell syndrome about 15 cases and review of literature
Nora Soumeya Fedala1, Ali El Mehdi Haddam2, Farida Chentli1, Djamila Meskine1, Nadia Kalafat1, Meriem Haddad1 & Fatima Saraoui1
Endocrinology, Bab el oued Hospital, Algiers, Algeria; Endocrinology, Bichat Hospital, Algiers, Algeria.

The Silver–Russell syndrome (SRS) is a sporadic heterogeneous disorder, clinically and genetically. The intrauterine growth retardation (IUGR), short stature because of lack of catch-up growth, relative macrocrania and limb asymmetry are the major diagnostic criteria, associated with a large number of clinical conditions. We report a case series of 15 cases with SRS, our goal is to relate the frequency of each symptom of the diagnostic criteria and evaluate the response to a long-term treatment by the GH. The diagnosis of SRS was established by the presence of three major criteria and (at least) two minor criteria. Indeed, all the patients showed short stature and relative macrocrania, and eight of them showed IUGR and body asymmetry. The paraclinical diagnosis (The GH deficiency) was confirmed in four of the cases. The treatment with GH whose efficacy was observed even in the absence of the deficit was reported in six cases. Although, SRS is a rare entity, it remains under-diagnosed. In spite of the clinical score for the diagnosis – recently established – its accuracy is largely influenced by the experience of the physician. Early diagnosis with initiation of treatment with GH is primordial to improve final height in adulthood.
DOI: 10.1530/endoabs.32.P635

Neuroendocrine disorders and anomalies of median line: about two cases
Fadila Saraoui, Nora Soumeya Fedala & Farida Chentli
Endocrinology, BAB El Oued Hospital, Algiers, Algeria.

Several observations brought reported a big frequency (12–50%) of pituitary insufficiency and abnormalities of the median line. The endocrine disorders are hypothamic origin and come along of pituitary ontogeny in more 30% of the cases. These abnormalities are associated with a defect of the embryological development of the bird nasofrontal which allows the development of various regions of the encephalon and the face. We report the observations of two boys KY 18 years old and 1 year old who presented to the birth a typical syndrome malformed of the median line (labiopalatine, flat nose, cleft lip, umbilical hernia) respectively. The two boys had severe short stature (~6 SDS and ~3 SDS respectively). The hormonal assessment highlighted a GH deficiency. Surgical correction was performed however the medical treatment by rGH was possible only height years later for KY and 2 years later for the other boy. The evolution is marked by the appearance of a thyreotrop insufficiency and insulin diabetes in KY. The existence of abnormalities of the median line at a child must be considered as a marker and introduce endocrine and neuroradiology investigations as well as long term follow. The appearance of the speed of growth, or signs of pituitary insufficiency need revaluation.
DOI: 10.1530/endoabs.32.P636

KISS1R mutations in normosmic congenital hypogonadotropic hypogonadism: clinical evaluation of two families and molecular characterization of a novel mutation
Frederic Brioude1,2, Jerome Bouligand1,2, Bruno Francou2,4, Jerome Fagart5,6, Ronan Roussel1, Says Viennchearan1,6, Laurent Combettes7, Sylvie Brailly-Tabard1, Marc Lombs3,4, Jacques Young1,4 & Anne Guijocho-Mantel1,2
1APHP Hopital Trousseau, Explorations Fonctionnelles Endocrinienes, Paris, France; 2APHP, Hopital Bicetre, Service de Génétique Moléculaire, Pharmacogénétique et Hormonologie, Paris, France; 3APHP, Hopital Bicetre, Service de Génétique Moleculaire et des Maladies de la Reproduction, Paris, France; 4Univ Paris-Sud, Faculté de Médecine Paris-Sud, Le Kremlin Bicetre, France; 5Univ Pierre et Marie Curie, Paris, France; 6Inserm UMR-S693, Le Kremlin Bicetre, France; 7Inserm UMR-S693, Hopital Bichat,Unique de l’Endocrinologie, Paris, France; 8Inserm U757, Orsay, France.

KISS1R mutations have been implicated in patients with normosmic congenital hypogonadotropic hypogonadism (nCHH) (OMIM #146110).
Objective
To describe in detail nCHH patients with biallelic KISS1R mutations belonging to two unrelated families, and to functionally characterize a novel KISS1R mutation.
Results
The p.Tyr313His original mutant was found in the homozygous state in three affected kindred (two females and one male) from a consangunous Portuguese family. This mutation, located in the seventh transmembrane domain, affects a highly conserved amino acid, perturbs the conformation of the transmembrane segment, and impairs MAP kinase signaling and intracellular calcium release. In the second family, a French Caucasian male patient with nCHH was found to carry two recurrent mutations in the compound heterozygous state (p.Leu102-Pro/Stop399Arg). In this patient, pulsatile GnRH administration restored pulsatile LH secretion and testosterone secretion, and long-term combined gonadotropin therapy induced spermatogenesis, enabling 3 successive pregnancies that resulted in two miscarriages and the birth of a healthy boy.
Conclusion
We show that a novel loss-of-function mutation (p.Tyr313His) in the KISS1R gene can cause familial nCHH, revealing the crucial role of this amino acid in KISS1R function. The observed restoration of gonadotropin secretion by exogenous GnRH administration further supports, in humans, the hypothalamic origin of the gonadotropin deficiency in this genetic form of nCHH. The possible role of KISS1R haploinsufficiency in miscarriage is discussed.
DOI: 10.1530/endoabs.32.P637

Strength training and testosterone treatment have opposing effects on migration inhibitor factor levels in ageing men
Dorte Glintborg1, Louise L Christensen1, Thue Kvorning2, Rasmus Larsen3, Kim Brixen4, David M Hougaard5, Bjorn Richelsen3, Jens M Bruun6 & Marianne S Andersen1
1Department of Endocrinology, Odense University Hospital, Odense, Denmark; 2Institute of Sport Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark; 3Department of Informatics and Mathematical Modelling, Technical University of Denmark, Kgs Lyngby, Denmark; 4Department of Clinical Biochemistry and Immunology, Statens Serum Institute, Copenhagen S, Denmark; 5Department of Internal Medicine and Endocrinology (MEA), Aarhus University Hospital, Aarhus, Denmark; 6Medical Department, Regional Hospital Randers, Randers, Denmark.

Objective
The beneficial effects of testosterone treatment (TT) in men with low normal testosterone levels are debated. Chemokine levels have not previously been evaluated during TT in combination with strength training (ST).

Design
A randomized, double-blinded, placebo-controlled study of 6 months TT (gel) in 54 men aged 60–78 years with bioavailable testosterone (BioT) < 7.3 nmol/l and waist circumference > 94 cm randomized to TT (50–100 mg/day, n = 20), placebo (n = 18) or ST (n = 16) for 24 weeks. Moreover, the ST group was randomized to TT (n = 7) or placebo (n = 9) after 12 weeks.

Methods
Clinical evaluation and chemokine measurements (migration inhibitor factor (MIF), monocyte chemotactic protein (MCP)-1, and macrophage inflammatory protein (MIP)-1α). Lean body mass (LBM) and regional fat mass (total, central and extremity) were established by dual x-ray absorptiometry and visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) were measured by magnetic resonance imaging.

Results
Following 24 weeks intervention, MIF and SAT were decreased during TT combined with strength training (ST). TT decreased fat mass (total, central, extremity, SAT) and increased BioT and LBM vs placebo. MIF levels increased during TT vs ST and SAT decreased during TT decreased fat mass (total, central, extremity) and increased BioT and LBM vs placebo.

Conclusion
The beneficial effects of testosterone treatment (TT) in men with low normal testosterone levels are debated. Chemokine levels have not previously been evaluated during TT in combination with strength training (ST).

DOI: 10.1530/endoabs.32.P638
P639

Decreased expression of four memory genes in non-syndromic cryptorchid testes
Faruk Hadziselimovic,1 Niels Omar Hadziselimovic1 & Philippe Demougin2
1Institute for Andrology, Liestal, Switzerland; 2LSTF Biozentrum, University of Basel, Basel, Switzerland.

Background
Egr1 has been widely recognized as essential for some aspects of learning and memory while Egr 4 has been shown to be involved in receptor – memory processes. Furthermore, it has been shown that testosterone enhances memory by increasing biological salience of incoming information. In cryptorchid boys, an elevated odd ratio for low IQ was found. i) It is postulated that the hypothalamus–pituitary–testicular axis is implicated in maintaining the similarity of gene expression between brain and the testis. Aim: We hypothesize that infertile cryptorchid males may have impaired expression of several memory genes in their testes.

Patients and methods
Whole genome analysis of testicular biopsies from seven boys who underwent orchiopexy with typical testicular histology of a high risk infertility group (HIR) were compared to 12 biopsies of cryptorchid boys with low risk for developing infertility (LIR). The HIR group had low or lack of expression of the following memory genes compared to LIR testes.

Conclusion
Impaired expression of four memory genes known to encode for proteins involved in signal pathways regulating cytoskeleton organization, synaptic vesicle transport and establishment of connections between neuronal cells may contribute to reduced intellectual and cognitive functions of cryptorchid males. The current findings provide new insight into potential molecular mechanisms into crucial processes for the development of these functions.

DOI: 10.1530/endoabs.32.P639

P640

Complete aromatase deficiency in four adult men: detection of a novel mutation and two known mutations in the CYP19A1 gene
Elisa Pignatti1, Kursad Unluhizarci1, Ermine Kartal4, Nahla Khawaja5, Cesare Carani1,2, Marco Marino1, Manuela Simoni1,2, Eleonora Vighi1 & Vincenzo Rochira1,3
1Chair and Unit of Endocrinology and Metabolism, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy; 2Integrated Department of Medicine, Endocrinology and Metabolism, Geriatrics, Azienda USL of Modena, Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy; 3Department of Andrology, Liestal, Switzerland; 4Department of Endocrinology and Internal Medicine, Erciyes University Medical School, Kayseri, Turkey; 5National Center for Diabetes, Endocrinology and Genetics (NCDEG), Amman, Jordan.

Introduction
At present, only eight men with loss-of-function mutations in the CYP19A1 gene have been described. Here we report the genetic study of four adult men with undetectable serum estrogens, unfused epiphyses, eunuchoid skeletal proportions, continuing linear growth, tall stature, genu valgum, osteoporosis, obesity and achondroplasia nigricans. Patient 1 (26-years/182 cm) and 2 (28-years/187 cm) are from Turkey with a history of consanguinity. Patient 3 (44-years/185 cm) and 4 (29-years/197 cm) are two brothers from Jordan without a history of consanguinity.

Methods
All coding exons with their flanking intronic sequences of CYP19A1 gene, amplified by PCR, were directly sequenced by ABI–Prism 3130 Genetic Analyzer and compared with known human CYP19A1 gene sequences.

Results
Patient 1 was homozygous for a point mutation in the first nucleotide of intron 3 (IVS3 + 1G > T); Patient 2 homozygous for a G > A mutation (c.1124 G > A) in exon IX resulting in protein missense mutation p.R375H. The two brothers (Patients 3 and 4) had a homozygous mutation in exon IV (c.434 G > A) leading to Arg to Glu substitution at position 115 (p.R115Q). All patients had impaired glucose tolerance. Patient 3 was diabetic. Patient 2 had a history of three forearm bone fractures after minimal trauma, Patient 1, 3, and 4 had impaired liver function and GH secretion.

Conclusions
The description of these new four aromatase-deficient men confirms the detrimental effects of congenital estrogen deficiency on glucose, liver and bone metabolism (particularly bone maturation and mineralization). The homozygous missense mutation in exon IV (p.R115Q) (Patients 3 and 4) is novel. Both aminoacids are basic, but their different conformational structure probably leads to tertiary or quaternary distortion in protein structure. The other two mutations have been previously described in heterozygosis and are found in homozygosis for the first time. Clinical evidence of documented osteoporotic fractures in an aromatase-deficient man is described for the first time.

DOI: 10.1530/endoabs.32.P640

P641

Mortality is increased in men treated with testosterone compared to age and sex-matched controls
Jesper Karmisholm1, Stine Eriksen2, Jorgen Runghol2 & Peter Vestergaard2
1Department of Medicine Endocrinology, Aalborg University Hospital, Aalborg, Denmark; 2Faculty of Medicine, Aalborg University, Aalborg, Denmark.

Aim and method
To assess the association between treatment with testosterone and the mortality in men with low testosterone levels in a large Danish population. Men treated with testosterone (n = 25 868) and age- and sex-matched controls (n = 51 736) were included. Follow-up concerned the development of cardiovascular events in a cohort of all men in Denmark filing prescriptions for testosterone in the period 1997–2008. Three age and sex-matched controls per patient were randomly selected from the background population. Information on mortality, disease, drug use and social variables was acquired using four Danish nationwide registries.

Results
Seven thousand three hundred and thirty-three testosterone users were identified. Women and prior (before 1997) testosterone users were excluded, generating a study cohort of 4792 cases (aged 46.3 ± 0.3, years (± S.E.M.) and 14 376 controls (46.7 ± 0.2 years), which was followed until December 2011. In the mean observation period (13.2 ± 0.03 years) 858/1963 deaths were observed in cases/controls yielding an unadjusted total mortality odds-ratio of 1.38 (1.26–1.51, 95% CI, P<0.01) in cases vs controls and correspondingly a Cox proportional hazard-ratio of 1.36 (1.25–1.47, 95% CI). Unadjusted odds-ratio for cardiovascular death was 1.22 (1.04–1.43, 95% CI) in cases vs controls.

Conclusion
We found a significant 36% increased mortality in men treated with testosterone compared to age- and sex-matched controls. We also found an increased risk of cardiovascular death in the cases. However, in this on-going study additional analyses are needed to further clarify whether the observed increased risk is connected with co-morbidity, concomitant drug.

DOI: 10.1530/endoabs.32.P641

P642

Seminal, ultrasound and psychobiological parameters correlate with metabolic syndrome in male members of infertile couples
Francesco Lotti, Giovanni Corona, Selene Degli Innocenti, Erminio Filimberti, Vittoria Scognamiglio, Linda Vignozzi, Gianni Forti & Matteo Magi
University of Florence, Florence, Italy.
Introduction
Metabolic syndrome (MetS) is a diagnostic category which identifies subjects at high risk for diabetes and cardiovascular diseases, erectile dysfunction (ED) and male hypogonadism. However, MetS impact on male infertility has been poorly studied. We systematically evaluated possible associations between MetS and clinical characteristics in men with couple infertility.

Methods
Out of 367 consecutive subjects, 351 men without genetic abnormalities were included. MetS was defined according to the IDF and AHA/NHLBI classification. All men underwent physical, hormonal, seminal and scrotal ultrasound evaluation. Erectile and ejaculatory functions were assessed by International Index of Erectile Function-15 erectile function domain (IIEF-15-EFD) and Premature Ejaculation Diagnostic Tool (PEDT), respectively, while psychological symptoms by Middlesex Hospital Questionnaire.

Results
Out of 351 patients, 27 (7.7%) fulfilled MetS criteria. Among ultrasound features, in an age-adjusted logistic model, only testis inhomogeneity was significantly associated with increasing MetS factors (HR = 1.36 (1.09–1.70), P < 0.01). In an age-adjusted model, MetS was associated with a stepped decline in total testosterone (TT) (B = −1.25 ± 0.33, P < 0.0001), without a concomitant rise in gonadotropins. At univariate analysis, progressive motility and normal morphology were negatively related to the number of MetS components (both P < 0.0001), but when age and TT were introduced in a multivariate model, only sperm morphology retained a significant association (B = −1.418 ± 0.42, P = 0.001). The risk of ED (IIEF-15-EFD score < 26) increased as a function of the number of MetS factors, even after adjusting for age and TT (HR = 1.45 (1.08–1.95), P < 0.02). No association between PEDT score and MetS was observed. Finally, after adjusting for age and TT, somatization and depressive symptoms were associated with increasing MetS components (B = 0.66 ± 0.03, P < 0.05; B = 0.69 ± 0.03, P < 0.02, respectively).

Conclusions
In men with couple infertility, MetS is associated with hypogonadism, poor sperm morphology, testis ultrasonad inhomogeneity, ED, somatization, and depression. Recognizing MetS could help patients to improve not only fertility but also sexual and overall health.

DOI: 10.1530/endoabs.32.P642

P643
Effects of iron therapy on pituitary gonadal axis and sperm parameters in adults with iron deficiency anemia (IDA)
Ashraf Soliman, Mohamed Yassin2, Osman Abdelrahmanm1, Vincenzo Desancis3 & Ahmed Elaww1
1Hamad Medical Center, Doha, Qatar; 2National Center for Cancer Care and Research, Doha, Qatar; 3Quisisana Hospital, Ferrara, Italy.

Objective
To evaluate semen parameters and measure serum FSH, LH, Testosterone (T) concentrations before and 6 weeks after i.v. 800–1200 mg elemental iron therapy in adults with iron deficiency anemia.

Patients and methods
This study investigated 11 adults with iron deficiency anemia (IDA) aged 40 ± 5 years, with full pubertal development (Tanner stage 5, eugonadal) and capacity to ejaculate. They had iron deficiency anemia mainly due to defective intake of iron. Anemia was diagnosed when Hb is < 10 g/dL. Serum iron, transferrin and ferritin concentrations confirmed the diagnosis of IDA. Basal serum concentrations of FSH, LH, and T were evaluated before and 6 weeks after i.v. iron therapy.

Results
After iv iron therapy and correction of anemia (Hb >11 g/dL) a significant increase of hemoglobin from 8.1 ± 0.17 to 13.2 ± 0.7 g/dL was associated with increased T (from 12.2 ± 1.4 to 15.0 ± 0.96 nmol/L), FSH (from 2.82 ± 0.87 to 3.82 ± 1.08 IU/L) and LH (from 2.27 ± 0.9 to 3.82 ± 1.5 IU/L).

Total sperm count (TSC) increased significantly from 72 ± 17.5 to 158 ± 49 million/mL (P < 0.001), sperm volume increased from 2.3 ± 0.6 to 2.6 ± 0.7 (P = 0.045), rapid progressive sperm motility (RPM) increased from 22.9 ± 9.4 to 69 ± 30 million/mL (P < 0.001), and sperms with normal morphology (NM) increased from 33 ± 5 to 56 ± 7 million/mL (P < 0.001).

Hemoglobin concentrations were correlated significantly with T (r = 0.75, P < 0.001), total sperm count (r = 0.81, P < 0.001), total progressive motility (r = 0.78, P < 0.001), rapid progressive motility (r = 0.74, P < 0.001) and sperms with normal morphology (r = 0.88, P < 0.001). Testosterone concentrations were correlated with TSC (0.52, P < 0.001), total progressive motility (0.55, P < 0.001) and RPM (0.55, P < 0.001) and NM (0.78, P < 0.001).

Conclusion
We proved that correction of anemia with i.v. iron therapy is associated with significant enhancement of sperm parameters and increased concentrations of serum T, LH, and FSH. These effects on spermatogenesis are reached by an unknown mechanism and suggest a number of pathways that need further human and/or experimental studies.

DOI: 10.1530/endoabs.32.P643

P645
Endocrine disruptors target ATP binding cassette transporters in the blood–testis barrier and impair Leydig cell steroidogenesis
Maurice J E Koekoek1,2, Anita C A Dankers2, Aldert H Piersma1,3, Frans G M Russel2, Martin van den Berg1, Rosalinde Masereeuw2 & Majorie B M van Duursen3
1Endocrine Toxicology Research Group, Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands; 2Department of Pharmacology and Toxicology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; 3Center for Health Protection, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands.

Efflux transporters in the blood–testis barrier (BTB) prevent entry and accumulation of xenobiotics in testis but are also involved in local transport of steroid hormones. Among these are the ATP-binding cassette (ABC) transporters, P-glycoprotein (P-gp/ABCB1) and multidrug resistance proteins 1 (MRP1/ABCC1) and 4 (MRP4/ABCC4). Here, we studied the interaction of suggested endocrine disruptors (EDCs) bisphenol A (BPA), tetra- and tri-brominated biphenyls A (TBBPA), bis(2-ethylhexyl) phthalate (DEHP), mono(2-ethylhexyl) phthalate (MEHP), perfluorooctanoic acid (PFOA), and perfluorooctanesulfonic acid (PFOS) with human P-gp, MRP1 and MRP4-mediated transport using membrane vesicles of human embryonic kidney (HEK293) cells overexpressing these transporters. Our data show that BPA, DEHP and MEHP, did not significantly alter P-gp, MRP1 and/or MRP4 activity. Both PFOA and PFOS inhibited the MRP4 activity by 50% and P-gp up to 25% at 100 μM. TBBPA showed complete inhibition of the three transporters at the highest concentration (100 μM) tested. To investigate the toxicological implications of transporter inhibition further, testosterone secretion and expression of steroidogenic genes were determined in mouse Leydig MA-10 cells upon exposure to EDCs. Only, BPA and TBBPA concentration-dependently induced testosterone secretion by MA-10 cells to 350 and 1000% of control at 10 μM, respectively. Blocking P-gp, using PSC833, further increased testosterone secretion after BPA and TBBPA exposure to 475 and 2000%, respectively. In contrast, the MRP inhibitor MK571 partly blocked testosterone secretion elicited by BPA (till 300%) and completely by TBBPA. Furthermore, expression of testis-specific steroidogenic genes StAR and CYP11A1 increased when exposed to EDCs in combination with transporter inhibitors. No effects on androgen receptor (AR) activation were found using an AR luciferase reporter assay. These data suggest that EDCs might affect male fertility by locally acting on the BTB and steroidogenesis. We propose that EDCs might disrupt local androgen production and transport from Leydig to Sertoli cells, thus potentially affecting normal germ cell development.

DOI: 10.1530/endoabs.32.P645
modulating testicular function in fetuses of 120 days of fetal age and in prepubertal sheep of 24 weeks of age. Males were born to mothers administered with either T propionate (T-males) or the vehicle (C-males). At both ages, histological parameters were quantified, and mRNA and protein expression of AMH and transcription factors involved in the AMH signaling as well as proteins related to the BT barrier were analyzed by RT-PCR and WB. Testicular weight was similar in fetal C-and T-males while was lower in prepubertal T-males. SC number was similar between T- and C-males fetuses, on the contrary, the SC number was increased and the number of GC was reduced in prepubertal T-males. mRNA expression of AP2 was similar in both groups and ages, but a higher expression of AMH was observed in T-males. The WB of AMH receptor (MISRII) was lower in T-males at both ages. N-cadherin protein expression was similar in T-and C-males fetuses, but lower in prepubertal T-males. Protein expression of connexin 43 was similar in fetuses, but higher in prepubertal T-males compared to C-males. These findings suggest that the altered environment impairing spermatogenesis of adult male sheep after PT exposure begins at prepubertal ages with an abnormal molecular and cellular environment. DOI: 10.1530/endoabs.32.P645

P646
Androgen levels and sexual activity in young men (n = 773), 20–29 years of age, a population based study. Odense Androgen Study
Line Velling Magnussen, Torben Leo Nielsen, Dorte Glintborg, Claus Hagen & Marianne Andersen
Odense University Hospital, Odense, Denmark.

Introduction
Low androgen levels are associated with decreased sexual activity. However, to our knowledge no population based study has evaluated the association between androgen levels and sexual activity in young men.

Aim
To evaluate associations between androgen levels and sexual activity in young men.

Design
Seven hundred and seventy-three Danish men, aged 20–29 years, underwent clinical and biochemical examination: Total testosterone (TT), bio-available testosterone (BioT) and DHT levels) and questionnaires (sexual function).

Results
391/773 (50.6%) were living with a partner. 141/773 (18.2%) were singles with a stable sexual partner and 241/773 (31.2%) were singles without a sexual partner. 391/773 (50.6%) were living with a partner. 141/773 (18.2%) were singles with a stable sexual partner and 241/773 (31.2%) were singles without a sexual partner. 28/773 (3.6%) were virgins.

TT, BioT and DHT levels were negatively associated with time since last coitus (r = −0.12, r = −0.10, r = −0.12, respectively; P < 0.001).

Four hundred and fourteen men reported lower frequency of coitus than desired. 204/414 had a partner and 99/204 criticized low libido in their partner. These 99 men had their last coitus 5 days ago (1–28) (median (10–90 percentiles)). The number of days since last coitus was 6 days (1–60) in the remaining complainers (105/204), who were content with their partner (P < 0.001 vs men unsatisfied with partner). The 99 men compared to the 105 men had significantly lower TT, BioT and DHT 19.1 vs 21.7 nmol/l; 11.2 vs 12.3 nmol/l and 1.55 vs 1.71 nmol/l, respectively (P < 0.01).

Conclusion
3.6% of men aged 20–29 years were virgins. Androgen levels were negatively associated with time since last coitus. Men with complaints concerning partner’s too low libido had fewer days since last coitus but had lower androgen levels than men who were satisfied with their partner.

DOI: 10.1530/endoabs.32.P646

P647
Abstract withdrawn.

DOI: 10.1530/endoabs.32.P647

P648
Characterization of sumoylated proteins in human sperm
Sara Marchiani, Beatrice Ricci, Lara Tamburinio, Monica Muratori, Marta Cambi, Daniele Nosi, Gianni Forti & Elisabetta Baldi
University of Florence, Florence, Italy.

SUMOylation is a post-translational protein modification involved in the regulation of essential cell functions. Our group found several SUMO-1 and SUMO-2/3ylated proteins in human ejaculated spermatozoa (Marchiani et al. 2011). We showed that SUMO-1 is mainly present in live spermatozoa and the percentage of SUMOylated spermatozoa was inversely correlated with total and progressive motility. SUMOylated proteins are mainly located in the nucleus and in the midpiece. To better understand the role of SUMO modification in sperm we aimed to characterize possible target proteins. In particular, we evaluated RanGap-1 (Ran GTPase-activating protein 1) one of the main target of SUMO in somatic cells, DRP1 (Dynamin-related protein 1), whose SUMOylation in somatic cells provokes alterations of mitochondrial functions, and Topoisomerase II alpha, necessary for chromatin condensation and demonstrated to be a target of SUMOylation in germ cells. By co-immunoprecipitation both with anti-SUMO-1 and with anti-RanGap-1 antibodies, we demonstrated that RanGap-1 is SUMO-1ylated in human sperm. With the same strategy, we showed that DRP-1 is SUMO-1ylated and that the SUMO modified protein is found at higher levels in sperm pools from asthenospermic men respect to normospermic. By confocal microscopy, we observed that the co-localization between SUMO-1 and RanGap-1 and between SUMO-1 and DRP1 are mainly found in the neck area. In addition, we also demonstrated the co-localization between SUMO-1 and Topoisomerase II in the sperm nucleus.

In conclusion, we identified RanGap-1, DRP-1 and Topoisomerase II as SUMOylation targets in human sperm. Our data suggest that SUMOylation could play different roles in human sperm functions and the characterization of target proteins is fundamental to reveal such roles. The higher levels of SUMOylated DRP1 in asthenospermic subjects, suggests that alterations in mitochondrial function due to SUMO-modified DRP1 may result in decreased sperm motility whereas sumoylation of RanGap may play a role in silencing gene translation.

DOI: 10.1530/endoabs.32.P648
and psychiatric comorbidity, respectively. Clinical data as well as a complete set of sexual hormonal profile were obtained. Controls were given the same questionnaires.

Results
Fifty three patients, 68% men with a median MELD 18, were included and compared to 22 controls. 96% had SD, which was more severe in older patients, those using spironolactone, and those suffering from anxiety. QOL was significantly impaired compared to controls. Central hypogonadism and hyperestrogenemia was present in most men. Blood levels of sexual hormones were similar in the alcoholic liver disease group compared to those of other etiology. In addition, low levels of DHEA-S were found in 97% of men. Total cholesterol and fractional cholesterol, precursors of sexual hormones correlated significantly with the level of total and free testosterone, free androgen index, SHBG and DHEA-Sulphate.

Conclusion
SD, an infra-estimated condition, is extremely common in cirrhotic patients awaiting LT. SD is likely a key factor in the impaired QOL typical of these patients. Factors associated with worsening of sexual function include advanced age, chronic spironolactone use and presence of anxiety disorders. Besides central hypogonadism, the reduced levels of DHEA, possibly due to adrenal dysfunction, is an aspect that deserves further investigation. Sexual dysfunction could, in part, be another manifestation of the recently coined ‘hepatosuderal syndrome’.

DOI: 10.1530/endoabs.32.P651

---

**P650**

Abstract withdrawn.

DOI: 10.1530/endoabs.32.P650

---

**P651**

Sexual dysfunction in cirrhotic patients awaiting liver transplantation

Agusin Ramos Prol, Beatriz Rodriguez Medina, Marina Berenguer Haym, Beatriz Leon de Zayas, Matilde Rubio Almanza, Vicente Campos Alborg & Juan Francisco Merino Torres

Hospital Universitario y Politécnico La Fe, Valencia, Spain.

Introduction

Data on sexual dysfunction (SD) in cirrhotic patients are limited. Sexual function is a complex area of human behavior with great impact on quality-of-life (QOL). Despite its relevance, it is rarely evaluated in clinical practice in cirrhotic patients. Indeed, published studies are heterogeneous, differ in the way sexual function is assessed, and usually evaluate only one specific aspect of sexual life. Our aim was to evaluate in detail the sexual function of patients with end-stage liver disease in the waiting list for liver transplantation (LT) and to compare it to that of a controlled group from the general population matched by age and gender.

Methods

Changes in sexual functioning questionnaire, Short Form 36 Health Survey and the Hospital Anxiety and Depression Scale were used to evaluate SD, QOL and psychiatric comorbidity, respectively. Clinical data as well as a complete set of sexual hormonal profile were obtained. Controls were given the same questionnaires.

Results

Fifty three patients, 68% men with a median MELD 18, were included and compared to 22 controls. 96% had SD, which was more severe in older patients, those using spironolactone, and those suffering from anxiety. QOL was significantly impaired compared to controls. Central hypogonadism and hyperestrogenemia was present in most men. Blood levels of sexual hormones were similar in the alcoholic liver disease group compared to those of other etiology. In addition, low levels of DHEA-S were found in 97% of men. Total cholesterol and fractional cholesterol, precursors of sexual hormones correlated significantly with the level of total and free testosterone, free androgen index, SHBG and DHEA-Sulphate.

Conclusion

SD, an infra-estimated condition, is extremely common in cirrhotic patients awaiting LT. SD is likely a key factor in the impaired QOL typical of these patients. Factors associated with worsening of sexual function include advanced age, chronic spironolactone use and presence of anxiety disorders. Besides central hypogonadism, the reduced levels of DHEA, possibly due to adrenal dysfunction, is an aspect that deserves further investigation. Sexual dysfunction could, in part, be another manifestation of the recently coined ‘hepatosuderal syndrome’.

DOI: 10.1530/endoabs.32.P651

---

**Table 1**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Endpoint: 15 years</th>
<th>P for ANOVA, last observation carried forward</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index (kg/m²)</td>
<td>31.8 ± 5.2</td>
<td>24.1 ± 3.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>114 ± 10.5</td>
<td>94.1 ± 8.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>103.0 ± 16.3</td>
<td>79.1 ± 12.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>157 ± 29</td>
<td>110 ± 19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>38.4 ± 15</td>
<td>39.6 ± 17.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>198 ± 33</td>
<td>149 ± 22.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>118 ± 29.7</td>
<td>91.2 ± 15.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RR systolic (mmHg)</td>
<td>148 ± 14</td>
<td>128 ± 11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RR diastolic (mmHg)</td>
<td>98 ± 11</td>
<td>81 ± 10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulse (bpm)</td>
<td>89 ± 9</td>
<td>75 ± 8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Conclusion
Intramuscular injections of testosterone undecanoate represent a feasible, safe and well tolerated modality of androgen substitution in hypogonadal men of a wide age range, substantiated by more than one decade of experience, facilitating a decrement of metabolic/cardiovascular risk factors.

DOI: 10.1530/endoabs.32.P652

P653
Metabolic syndrome correlates with prostate volume and biochemical and ultrasound signs of prostate inflammation in male members of infertile couples
Francesco Lotti, Giovanni Corona, Linda Vignozzi, Matteo Rossi, Elisa Maseroli, Mauro Gacci, Gianni Forti & Mario Maggi
University of Florence, Florence, Italy.

Introduction
The impact of metabolic syndrome (MetS) on male infertility has been poorly studied. We recently reported that MetS is associated with hypogonadism, poor sperm morphology and tests ultrasound inhomogeneity. However, the possible associations between MetS and prostate-related symptoms and signs are still lacking.

Methods
Out of 351 subjects without genetic abnormalities previously evaluated for couple infertility, clinically microcytic anemia, normal semen analysis and 171 underwent also ultrasound and are here analysed. MetS was defined according to NCEP-ATPIII classification. All men underwent hormonal (including total testosterone (TT) and insulin), seminal and transrectal ultrasound evaluation. Prostate-related symptoms were assessed by National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) and International Prostate Symptom Score (IPSS).

Results
Out of 171 patients, 22 (13%) fulfilled MetS criteria. In an age-adjusted regression model, insulin levels increased as a function of MetS components (β = 0.134, P < 0.0001) and showed an inverse correlation with TT (adj. r = −0.359, P < 0.0001). In an age-TT-insulin-ordinal regression model, normal morphology was negatively related to the number of MetS components (β = −0.083, P < 0.002). At univariate analysis, the number of MetS components was weakly associated with NIH-CPSI void subdomain (r = 0.110, P < 0.05) and IPSS (r = 0.143, P < 0.05) score, however not confirmed after adjusting for confounders. Using an age-TT-insulin-adjusted model, a positive correlation between the number of MetS components and sIL-8 levels was observed (β = 0.760, P < 0.05). When transrectal ultrasound features were evaluated, using an age-TT-insulin-adjusted ordinal regression model, the number of MetS components was positively related to prostate volume (β = 0.086, P < 0.0001), arterial prostatic peak systolic velocity (β = 0.148, P < 0.02), prostate inhomogeneity severity (β = 0.521, P < 0.01) and prostate calcification size (β = 0.087, P < 0.02). No association between MetS and seminal vesicles features was found.

Conclusions
In men with couple infertility, MetS is positively associated with a higher prostate volume, biochemical (sIL8) and ultrasound signs of prostate inflammation, but not with prostate-related symptoms.

DOI: 10.1530/endoabs.32.P653

P654
Identification of vitamin D (VDR) and retinoic X (RXR) receptor in normal and neoplastic human reproductive tissues
Federica Cariati1, Vincenzo Gigantino2, Giorgio Coppola1, Claudia Pivonello1, Mariano Galdiero1, Giuseppe Bedi, Andrea Lenzi2, Renato Franco2, Annamaria Colao1 & Rosario Pivonello1
1Section of Endocrinology, Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy; 2Pathology Unit, National Cancer Institute, Pascale Foundation, Naples, Italy.

Background
Vitamin D is an important modulator of cell growth, differentiation and death in normal and neoplastic cells. Its actions are mediated by vitamin D receptor (VDR), which heterodimerizes with nuclear retinoid X receptors (RXRs). Recently, it has been suggested that vitamin D system have a role in male reproduction. The aim of this study was to investigate the VDR and RXRs localization in normal and neoplastic human male reproductive tissues.

Methods
Identification of VDR and RXRs was performed by immunohistochemistry and immunofluorescence on epididymal, seminal vesicle, testis and prostate homogenates and on two tissue arrays (TMA) platforms. TMAs were built using the most representative areas from testicular germ cell cancer (TGCTs) samples (15 carcinomas in situ, 25 embryonal carcinomas, 39 seminomas, 5 choriocarcinomas, 15 teratomas, and 15 Yolk sac tumours) and from 40 cases of prostate cancer (PC).

Results
VDR and RXRα were expressed in epididymis, seminal vesicle and prostate tissues. VDR showed membrane-cytoplasmic immunoreactivity while RXRα showed a cytoplasmic localization. In normal testis, VDR was expressed in Sertoli cells and in epithelium of rete testis while RXRα was detected in Leydig, Sertoli and spermatogonia cells. Membrane VDR immunostaining was strong in differentiated TGCTs while RXRα localization was much more positive in undifferentiated TGCTs. Notably, VDR showed high expression in healthy prostate (80% ± 0) compared to PC tissues (64% ± 16.8). Moreover, VDR expression decreased in tumours with high Gleason score (GS) (67% in GS < 7, 50% in GS = 7 and 30% in GS > 7) and in these latter VDR was localized exclusively on membrane.

Conclusions
VDR and RXR are expressed in different tissue of the reproductive system and tumours, suggesting a role of vitamin D in reproduction and/or in the development of tumors. Membrane VDR localization suggest a non-genomic role of VDR in prostate and tests tumour tissues.

DOI: 10.1530/endoabs.32.P654

P655
Fat boosts, while androgen receptor activation counteracts, BPH-associated prostate inflammation
Linda Vignozzi1, Mauro Gacci2, Ilaria Celli3, Raffaella Santi4, Giovanni Corona5, Anna Maria Morelli2, Giulia Rastrelli5, Paolo Cozzaglio5, Arcangelo Sebastianelli2, Elena Maneschi2, Paolo Carini6 & Mario Maggi1
1Sexual Medicine and Andrology Unit, University of Florence, Florence, Italy; 2Endocrinology Unit, Azienda USL Maggiore Bellaria Hospital, Bologna, Italy; 3Ospedale Sant’Andrea, University La Sapienza, Rome, Italy; 4Urology Unit, University of Florence, Florence, Italy; 5Pathological Anatomy Unit, University of Florence, Florence, Italy; 6Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy; 7Diabetic Section Geriatric Unit, University of Florence, Florence, Italy.

Background
Metabolic syndrome (MetS) and benign prostate hyperplasia (BPH) are often comorbid. Chronic inflammation, a determinant pathogenic factor for BPH, is a putative link between the two conditions.

Methods
In a multi-center cohort of BPH patients (n = 244) who underwent prostatectomy, we evaluated whether MetS is associated with prostate inflammation in BPH specimens. In addition, we investigated the in vitro inflammatory effects of metabolic insults on human prostate myofibroblasts (hBPH).

Results
Inflammatory infiltrates score (IS) in prostatectomy specimens showed a stepwise association with the number of MetS factors present (P = 0.001). After adjusting for age, reduced HDL cholesterol and elevated triglycerides were the only factors significantly associated with IS. Increased IS was also significantly associated with hypogonadism. In an age- and testosterone (T) - adjusted model, dyslipidaemia was still associated with IS.

To investigate whether metabolic factors could directly trigger prostate inflammation, we performed preliminary studies in myofibroblastic hBPH. Among the different factors, oxidized low-density lipoprotein (oxLDL) showed the highest secretion of IL-8 (> 10-folds) – a surrogate marker of prostate inflammation as well as IL-6, and bFGF. Co-treatment with DHT significantly inhibited oxLDL-induced secretion of IL-8, whilst an AR-antagonist, bicalutamide, reversed DHT effects. DHT suppresses oxLDL receptor (LOX-1) expression.

Conclusions
Our data suggest that fats and insulin could have a detrimental effect on prostate health, boosting inflammation, a key pathogenic factor in BPH. Conversely, beneficial effects of DHT in counteracting lipid- and insulin-induced prostate alterations, suggest that T – via its conversion into DHT – may have unexpected beneficial effects on prostate health.

DOI: 10.1530/endoabs.32.P655

Endocrine Abstracts (2013) Vol 32
CATSPER is a family of sperm-specific calcium channels activated by P in human spermatozoa (Lishko et al. 2011, Strunker et al. 2011). KO mice for CATSPER are infertile due to severe defects in sperm motility.

To verify whether, in a large sample of male subjects seeking medical care for sexual dysfunction (SD), prostate-specific antigen (PSA) might represent a reliable marker of testosterone bioactivity, even downstream to its receptor binding.

In our recent study (Jin et al. 2011) reporting physiological AR occurs during transit in the cumulus matrix of the oocyte (where P is present at µM concentrations) before sperm attachment to the zona pellucida, our data suggest that CATSPER may be considered a possible molecular target for the development of novel therapeutic strategies for male infertility as well as for male-directed contraception.

Conclusions
PSA is a reliable marker of T biological activity and it may represent a new tool in detecting clinically relevant hypogonadism. The single, costless determination of PSA levels might give insights not only on the circulating levels of total T, but also on its active fractions and, most importantly, in androgen receptor bioactivity.

DOI: 10.1530/endoabs.32.P658

Effects of testosterone replacement therapy on hepcidin levels in young hypogonadal men
Vincenzo Palumbo1, Dario Esposito1, Daniela Visconti1, Adele Topa1, AnitaLa Rezza1, Giuseppe Bellastella2, Annamaria De Bellis2 & Antonio Agostino Sinisi1
1Dpt Scienze Cardiotoraciche e Polmonari, Second University of Napoli, U. Endocrinology, Napoli, Italy; 2Dpt Internistica Clinica e Sperimentale Magrassi-Lanzara, Second University of Napoli, Napoli, Italy.

Erythrocytosis is a frequent adverse event associated with testosterone (T) administration in aged hypogonadal men, but the mechanisms involved remain poorly understood. T administration to aged men reduced hepcidin (Hpc) levels, a cytokine regulating iron availability, suggesting a potential role in deregulated erythropoiesis. Aim of present study was to evaluate the effects of T replacement therapy on Hpc levels in young hypogonadal men.

DOI: 10.1530/endoabs.32.P659

Endocrine Abstracts (2013) Vol 32
Methods
Fifty-eight subjects (18–36 years) with hypogonadism due to Kallmann syndrome (16), idiopathic hypogonadism (12), multiple pituitary deficiency (7), Klinfelter syndrome (18), and anorchidism (5) were studied. Blood samples were obtained basally (pts. never treated or after 3-months suspension) and after 6–12 months of T substitution therapy with 1 g of T undecanoate (TU) i.m. every 10–12 weeks (30 cases), or 250 mg of T enanthate (TE) i.m. every 2–3 weeks (20 c), or 50–100 mg T gel/d (6 c). In all samples haematocrit (Hb), Hpc (by Elisa) and T (by RIA) were determined. T therapy increased T and Ht, and decreased Hpc levels (P < 0.001). Hpc levels were negatively related to T and Ht. Fifteen subjects (26%) developed polycythaemia (Ht > 50%); 10 out 15 (67%) received TE.

Conclusion
Erythrocytosis is also frequent in T treated young hypogonadic. TE administration seems favour polycythaemia respect to other formulations. T-induced suppression of Hpc may contribute mechanistically to stimulate erythropoiesis.

DOI: 10.1530/endoabs.32.P659

P660
D3 levels and hypogonadism in men
Adriana Banarova, Zuzana Zelinkova & Juraj Payer
Comenius University, Bratislava, Slovakia.

Objective
25-OH vitamin D3 (D3) possibly affects testosterone production. In some cross sectional studies the level of D3 correlates positively with total testosterone (TT) and free androgen index (FAI). In the European Male Ageing Study positive association of D3 with secondary and compensated hypogonadism was confirmed.

Aim
The aim of the study was to determine the relationship between D3 levels and levels of TT, LH, FSH and FAI in men. Secondary aim was to assess seasonality of measured values of D3, TT a FAI.

Methods
In 72 men with average age 68 years admitted to 5th Department of Internal Medicine we determined levels of D3 by chromatography, TT, LH and FSH by electrochemiluminescence and calculated FAI (TT/SHBG × 100). Patients with severe liver disease, malignancy, antiandrogen therapy and vitamin D3 supplements were excluded. The correlation statistic was done by MedCalc system for all measured values and specifically for values in physiological range.

Results
The average level of TT was 13.3 nmol/l (interval 1–31.7 nmol/l), FAI 37% (10–88.2%), FSH 9.3 IU/l (1.3–41.1), LH 7.3 IU/l (2.1–34.1) and D3 23.1 µg/l (4–52.5 µg/l). We did not confirm correlation of D3 with androgen levels in whole group. In subgroup with values in physiological range we found negative correlation of D3 with FSH (r = 0.11, P = 0.02) and LH (r = 0.1, P = 0.02). We found insignificantly higher levels of TT in summer comparing with winter but we did not find any seasonality in FAI and D3 levels.

Conclusion
In our study we did not confirm correlation of D3 with TT, FAI, FSH and LH in whole group but we confirmed negative correlation of D3 and FSH and LH in subgroup with values in physiological range. In this sample, we confirmed association of D3 levels and compensated hypogonadism similarly as in European Male Ageing Study.

DOI: 10.1530/endoabs.32.P660

P661
Changes of neuroactive steroids caused by the smoking discontinuance
Michaela Duskova1, Hana Hruskovcova1, Martin Hill1, Hana Pospisilova1, Eva Kralikova1 & Luboslav Starka1,2
1Institute of Endocrinology, Prague, Czech Republic; 23rd Department of Medicine, First Faculty of Medicine, Tobacco Dependence Treatment Centre, Prague, Czech Republic.

Introduction
Tobacco dependence is considered to be a serious psycho-social problem. Chronic smoking can cause fertility disorders with both sexes. The literature brings up contradictory results in relation to the effects of the smoking on the steroid hormones levels. Only a few papers discuss the effect of the nicotine addiction treatment.

Methods
We observed 26 smokers who decided to quit smoking and abstained from smoking for one year. With everyone thorough anamneses were written down, basic anthropometric data measured and at the smoking period their blood samples taken. Further samples were taken after 6, 12, 24 and 48 weeks starting with the beginning of the smoking abstinence. We measured anthropometric data, levels of steroid hormones and their neuroactive metabolites by GC–MS, LH, FSH, SHBG mg every etabolites by GC–MS; LH, FSH, SHBG using RIA during every examination. The abstinence was verified measuring the CO amount in the exhaled air and determining cotinine in their urine. The local Ethics Committee approved the study. All patients have signed an informed consent form before taking part in the study.

Results
We observed the effect of smoking abstinence on the steroid spectra with the men successful in abstaining from smoking. After a one-year abstinence the statistically significant increase in SHBG that decreased only after 6 weeks and stayed constant. Testosterone and some other androgens had been decreasing continually during the whole first year of abstinence. Also FSH decreased along with the decreasing testosterone level. The changes in SHBG and testosterone did not correlate with BMI apparently this is a direct effect of the smoking discontinuance.

Conclusion
After the smoking discontinuance SHBG, testosterone and other androgens decreased. This indicates the complex effects of smoking.

Acknowledgement
The study was supported by grant IGA MZCR 12340-5, 13890 and 11277.

DOI: 10.1530/endoabs.32.P661

<p>| Table 1: PSA levels in patient treated with testosterone undecanoate 1000 mg at 3 months till 4 years. |
|----|----|----|----|----|----|----|</p>
<table>
<thead>
<tr>
<th>T0</th>
<th>T1–2 weeks</th>
<th>T2–3 months</th>
<th>T3–6 months</th>
<th>T3 bis 4 years</th>
<th>T4–1 year</th>
<th>T5–2 years</th>
<th>T6 3 years</th>
<th>T7–4 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>1.76</td>
<td>2.87</td>
<td>2.45</td>
<td>2.81</td>
<td>2.20</td>
<td>2.00</td>
<td>1.90</td>
<td>1.68</td>
</tr>
<tr>
<td>P</td>
<td>0.06</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>No</td>
<td>106</td>
<td>14</td>
<td>9</td>
<td>12</td>
<td>10</td>
<td>85</td>
<td>41</td>
<td>36</td>
</tr>
<tr>
<td>T value vs T0</td>
<td>0.22</td>
<td>0.44</td>
<td>0.31</td>
<td>0.67</td>
<td>0.59</td>
<td>0.76</td>
<td>0.61</td>
<td>0.59</td>
</tr>
</tbody>
</table>
**Table 2** Correlation age and prostatic volume with PSA in TUD treatment till 4 years.

<table>
<thead>
<tr>
<th>Observation</th>
<th>At 1 year</th>
<th>At 2 years</th>
<th>At 3 years</th>
<th>At 4 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before TUD</td>
<td>0.94</td>
<td>0.33</td>
<td>0.31</td>
<td>0.15</td>
</tr>
<tr>
<td>After 1 year TUD</td>
<td>0.60</td>
<td>0.49</td>
<td>0.55</td>
<td>0.42</td>
</tr>
<tr>
<td>After 2 years TUD</td>
<td>0.60</td>
<td>0.49</td>
<td>0.55</td>
<td>0.42</td>
</tr>
<tr>
<td>After 3 years TUD</td>
<td>0.60</td>
<td>0.49</td>
<td>0.55</td>
<td>0.42</td>
</tr>
<tr>
<td>After 4 years TUD</td>
<td>0.60</td>
<td>0.49</td>
<td>0.55</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Conclusions

1. Testosterone undecanoat 1000 mg injectable i.m. at 3 months does not increase significantly PSA level after 4 years administrations.
2. PSA level post testosterone is in fact dependent on age, prostatic volume before treatment and the level before treatment.

DOI: 10.1530/endoabs.32.P662

**Table 3** Multiple regression test.

<table>
<thead>
<tr>
<th>Observations</th>
<th>R²</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year TUD</td>
<td>0.52</td>
<td>24.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>After 2 years TUD</td>
<td>0.75</td>
<td>34.28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>After 3 years TUD</td>
<td>0.83</td>
<td>47.84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>After 4 years TUD</td>
<td>0.83</td>
<td>6.5</td>
<td>0.0509</td>
</tr>
</tbody>
</table>

**P663**

Analysing by decade, testosterone undecanoat depot injectable does not increases prostate volume. Study during up to 6 years on hypogonadic patients

Dan Peretianu1, Mara Carsote2, Catalina Poiana2, Daniela Cristina Staicu1 & Matei Pisoschi3
1Societatea Civila Medica Povernei, Bucharest, Romania; 2C.I. Parhon Institute of Endocrinology, Bucharest, Romania; 3Burghelie Hospital, Bucharest, Romania.

**Aim**

Re-analysing the effect of injectable testosterone undecanoat depot (TUD) in hypogonadic patients.

**Material-method**

i) Patients: at 175 men with hypogonadism (median age: 64 years).
ii) Distribution: by decade.
iii) TUD (Nebido-Bayer-Schering) 1000 mg was injected once per 3 months i.m.
iv) Prostate volume (PV) appreciated by per-abdominal ultrasound: 3.5 MHz probe, elliptical volume (cm³), Aloka 550.
v) Time of analysis: before starting testosterone (T0), after 1/2 month (T1), 3 (T2), 6 months (T3), 1 (T4), 2 (T5), 3 (T6), 4 (T7), 5 (T8), 6 years (T9).
vi) Maximum increment from T0 was noted Δ M %.

**Results**

i) All average prostatic volume for decade in Table 1.

**Discussion**

The more severe forms of Leydig cell hypoplasia are characterized by predominance of female external genitalia and absence of secondary sexual differentiation in puberty. Milder forms have predominantly male external genitalia, micropenis/hypospadias, or infertility without sexual ambiguity. It is biochemically characterized by low testosterone levels, without elevated precursors, even after stimulation with human chorionic gonadotropin, and LH increased levels.

DOI: 10.1530/endoabs.32.P662

**P666**

Male pseudohermaphroditism Leydig cell hypoplasia

Sandra Belo1,2, Angelo Magalhães1,2 & Davide Carvalho1,2
Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar de São João, Porto, Portugal; 3Faculty of Medicine, University of Porto, Porto, Portugal.

**Introduction**

LH receptor plays an important role in sexual development and reproductive function. Mutations of this receptor lead to the development of three clinical conditions: Leydig cell hypoplasia, hypergonadotropic hypogonadism with primary amenorrhea and familial male limited precocious puberty. The first two entities result from inactivating mutations. In Leydig cell hypoplasia, with autosomal recessive inheritance, the phenotypic spectrum correlates with the degree of residual activity of mutated receptor.

Case

Thirty six years old patient, referred for evaluation of primary amenorrhea. It presented history of pubarche at 13 years old and absent thelarche (breast development only after estro-progestative therapy), family history of primary amenorrhea in a 1st degree, paternal line, cousin. The examination showed breast development on Tanner’s stage III, sparse pubic hair, female external genitalia and single, bilateral inguinal masses. Chromosome study revealed to be a 46XY individual. Analytically the patient presented FSH 15.59 mIU/mL, LH 35.71 mIU/mL, prolactin 3.1 ng/mL, estradiol 24.0 pg/mL, total testosterone 0.10 ng/mL and 17-hydroxy-progesterone 0.96 ng/mL. The MRI showed an image suggestive of vagina and in the inguinal regions images suggestive of testicles, ovaries were not identified. Human chorionic gonadotrophin stimulation test was performed with the following results: Testosterone 0.08 (0.08 mg/mL and 17-OH-progesterone 0.94 (0.41 ng/mL. The patient underwent orchietomy.

**Discussion**

Histological exam revealed presence of testicular parenchyma devoid of germ cells and absence of Leydig cells. Search for mutations of the LH receptor is ongoing.

**P665**

Immunohistochemical detection of Prok1 and ProkR1 in normal testis and germ cell tumour tissue microarrays

Vincenzo Gigantino1, Renato Franco1, Paolo Chieffi1, Vincenzo Palumbo1, Iolanda Cioffi3, Adriana De Massi1 & Antonio Agostino Sinisi3
1Dpt Pathologia, INT Fondazione Pascale, Napoli, Italy; 2Dpt Psicologia, Second University of Napoli, Napoli, Italy; 3Dpt Scienze Cardiorespiratorie e Polmonari, Second University of Napoli, U. Endocrinology, Napoli, Italy.

Prokinetins (Prok1 and Prok2) are chemokine-like peptides, which regulate through two G-protein-coupled receptors, ProkR1 and ProkR2, different physiological and pathological functions. Prok1 plays a significant role in tumour development and progression in several tissues. There are few data on the involvement of Prok1 and ProkR1 in testicular cancer. Aim of this study was to evaluate the expression of Prok1 and ProkR1 in a series of testicular germ cell tumours (GCT).

**Materials and Methods**

We evaluated by immunohistochemistry the expression of Prok1 and ProkR1 in 2 Tissue Micro Array (TMA), containing a series of 140 GCT (90 seminomas, S, and 50 mixed non-seminomas, NS) and 30 normal tissues. We selected all representative areas of each component of NS (embryonic carcinoma, EC, yolk sac tumour, YS, chorioncarcinoma, CH, teratoma, T, and carcinoma in situ, CIS).

**Results and conclusions**

Prok1 absent in normal germ cells resulted frequently expressed in GCT (78% S, 58% NS, 83% CIS), with higher level in S than in other types (P < 0.005). ProkR1 was poorly expressed in GCT, except for EC (50% were positive). No correlation

DOI: 10.1530/endoabs.32.P665
was observed between ligand and its receptor presence. The expression of Prok1-ProkR1 system in GCT suggests a potential role as autocrine pathway in the development and progression of a subset of these tumours.

DOI: 10.1530/endoabs.32.P665

P666
Endocrine disruptors in seminal fluid: bisphenol A, triclosan and benzophenone-3
Marianna Krause, Hanne Frederiksen, Kristian Almstrup, Niels E Skakkebaek, Anders Juul & Anna-Maria Andersson
Department of Growth and Reproduction, Rigshospitalet, Copenhagen, Denmark.

Introduction
There is concern that unintended environmental exposures to numerous chemicals, including bisphenol A (BPA), triclosan (TCS) and benzophenone-3 (BP-3), all of which can be detected in serum and urine, may have adverse endocrine effects on human reproduction. Less is known about the concentrations of these chemicals in other body fluids. Here we present data, which show that these three chemicals can also be present in seminal fluid of young men.

Materials and methods
From an ongoing study on male reproductive function in young men from a general population, we selected 28 men with high urinary excretion of BP-3, which were examined in 2007 and from which both serum and seminal fluid were available for chemical analysis. Serum and semen samples were collected within one hour. Samples were analyzed for TCS, BPA, and BP-3 by TurboFlow LC–MS/MS.

Results
BPA, TCS, and BP-3 were detected in respectively 54, 18, and 29% of the seminal fluid samples in concentrations ranging from \( \text{LOD}, 8.470 \text{ ng/ml} \) (BPA); \( \text{LOD}, 6.654 \text{ ng/ml} \) (TCS); and \( \text{LOD}, 18.236 \text{ ng/ml} \) (BP3) respectively. Thus, some subjects had extremely high levels in seminal fluid. The five men with the highest concentrations of TCS and BP-3 in serum also had the highest concentrations of TCS and BP-3 in seminal fluid. In some men the concentrations of BP-3 were higher in the seminal fluid sample than in the serum sample.

Conclusion
BPA, TCS, and BP-3 were detected in seminal fluid from a significant proportion of young men from a general population. We do not know whether the seminal plasma content of BP-3, TCS, and BPA originate from rete testis fluid, the epididymis, the prostate or the seminal vesicles. It remains to be seen whether the presence of these chemicals in seminal fluid is associated with effects on testicular hormones, sperm cell function, or the female reproductive tract.

DOI: 10.1530/endoabs.32.P666

P667
Sperm DNA fragmentation as assessed by TUNEL/PI: mean values in fertile men and intra individual variability
Monica Muratori, Lara Tamburrino, Marta Cambi, Sara Marchiani, Ilaria Natali, Ivo Noci, Mario Maggi, Gianni Forti & Elisabetta Baldi
University of Florence, Florence, Italy; ¹Ospedale d Pescia, Pescia, Italy.

Tests detecting sperm DNA fragmentation (SDF) could be included in the clinical management of male infertility. TUNEL/PI is an innovative version of the TUNEL assay, and it is able to distinguish between two different populations: PI brighter and PI dimmer sperm. The aims of the study were to determine the average value of SDF in recruited men of proven fertility and to verify whether SDF discriminates between fertile and subfertile men independently from semen quality. In addition, we investigated the intra-individual coefficients of variation (CV) of SDF, by comparing two consecutive measures of SDF in the same patients. We found that in 67 recruited fertile men the average value of SDF was 35.8 ± 14.8%. After matching fertile (n = 58) to 99 sub fertile men (ratio 1:(1–3)) for age and semen quality, we observed that total SDF was significantly higher in the group of patients (44.5 ± 917.2%) than in fertile subjects (36.3 ± 14.8, \( P < 0.005 \)) and such a difference was totally due to SDF of PI brighter sperm (respectively; 27.4 ± 13.0 vs 20.8 ± 9.2, \( P < 0.001 \)) since SDF in PI dimmer population was similar in the two groups. Regarding the intra-individual CVs of SDF, they were quite low (8.9 ± 5.8%, n = 11) within 3 months and resulted lower than any conventional semen parameter. When the length between the two determinations of SDF was >3 months, the intra-individual CV for SDF increased to 17.1 ± 15.0%, n = 42. In conclusion, we demonstrated that SDF in PI brighter provides information on male infertility additional to those obtained by routine semen analysis. These results encourage us to continue the collection of fertile men to the aim of building the reference value for SDF as assessed by TUNEL/PI. In addition, we reported that within 3 months, SDF is the most stable intra-individual semen parameter.

DOI: 10.1530/endoabs.32.P667
P668
The identification of pre-diabetes condition with ARIC algorithm, predicts long-term CV events in patients with erectile dysfunction
Giovanni Corona1, Giulia Rastrelli2, Antonio Silverii2, Gianni Forti2, Edoardo Mannucci2 & Mario Maggi2
1Endocrinology Unit, Maggiore Hospital, Bologna, Italy; 2Sexual Medicine

Introduction
The Atherosclerosis Risk in Communities (ARIC) algorithm is one of the most efficient instruments for the prediction of incident type 2 diabetes (T2DM). Recently it has been shown to predict another relevant cardiovascular (CV) risk factor, such as chronic kidney disease. The aim of the present study is to verify whether, in patients with erectile dysfunction (ED), the use of ARIC diabetes risk score might improve the efficacy in predicting major CV events of other CV risk algorithms specifically developed for the assessment of CV risk.

Methods
A consecutive series of 2437 men (mean age 52.5 ± 12.9 years) attending our outpatient clinic for sexual dysfunction was retrospectively studied. A subset of this sample (n = 1687) was enrolled in a longitudinal study (mean follow up of 4.3 ± 2.6 years). The assessment of metabolic risk was evaluated with the ARIC algorithm. The assessment of CV risk was evaluated using the Progetto Cuore risk engine.

Results
In the cross sectional study ARIC score was inversely related with testosterone levels, sexual functioning and penile blood flow. When longitudinal sample was analyzed, higher baseline ARIC score significantly predicted MACE even when subjects with diabetes mellitus at baseline were excluded from the analysis (HR = 1.522 (1.086–2.135), P = 0.015 for trend). In addition, among subjects classified as ‘low-risk’ (CV risk <20% at 10 years corresponding to <9% at 4.3 years) by Progetto Cuore, a ROC curve analysis for ARIC (vs MACE) allowed the identification of a threshold of 0.22, which had a positive predictive value for 4.3-year MACE of 9%. Applying the ARIC score (with a threshold of 0.22) to Progetto Cuore ‘low risk’ subjects, we could classify as ‘at high risk’ 89.8% of subjects with incident MACE vs 79.6% with Progetto Cuore only.

Conclusions
In patients with ED identifying pre-diabetes, even with algorithms, predicts long-term CV events.

DOI: 10.1530/endoabs.32.P668

P669
Is pericentromeric inversion of the heterochromatic region of chromosome 9 involved in couple infertility?
Oana-Monica Popa, Corina Neamtu & Adriana Padure
C. I. Parhon National Institute of Endocrinology, Bucharest, Romania.

Pericentromeric inversion of the heterochromatic region of chromosome 9 has been reported in almost 4% of the cases of male infertility.

Objective
Determining the karyotype from an infertile couple scheduled to perform IVF.

Materials and methods
Slides with metaphasic chromosomes were GTG-banded according to standard protocol for cytogenetic analysis (karyotype). FISH analysis – inverted DAPI (4’-6-diamidino-2-phenylindole) staining was used to confirm the anomaly in chromosome structure.

Results
The karyotype revealed modification of the heterochromatic region of both chromosomes in the male partner. The karyotype for female partner was normal. In case of male partner we suspected the pericentromeric inversion of the heterochromatic region of the long arm (q) of chromosome 9. Using Inverted-DAPI staining we confirmed the inversion on both chromosomes.

Conclusion
Karyotyping followed by FISH is useful to select appropriate couples to improve the success rate of IVF.

Further investigation of the hormonal profile and seminal liquid analyses for male partner will show the involvement of the chromosomal abnormality in the hypothalamic–pituitary–testicular axis.

DOI: 10.1530/endoabs.32.P669

P670
The hypothalamus–hypophysis–gonads axis in men in reproductive age with obesity and different pituitary adenomas
Yulduz Urmanova & Iroda Nabieva
Tashkent Pediatric Medical Institute, Bogishamol 223, Tashkent 100140, Uzbekistan.

The aim
To study of functional status of hypothalamic–hypophysis–gonads axis men in reproductive age with obesity and different pituitary adenomas (PA).

Materials and methods
We examined 44 males with obesity 1–3 degrees with associated pathology (11 of them – pro and 33 – retrospectively). Mean age of patients was 22.9 years old. Control group constituted by 20 healthy men with different age.

All patients underwent clinical and biochemical evaluations including endocrine check, lipids profile, hormonal profile (LH, FSH, prolactin, sex steroid binding globulin, and free testosterone), genitalia ultrasonography, height, body mass, waist circumference (WC), hip circumference (HC), waist–hip ratio, questioning, and other studies.

Results
On the base of etiology of adenoma we found following: non-functional PA, 34 patients (77.3%); corticotropinoma, 5 (11.4%); craniofaryngioma, 4 (9.0%); and somatotropinoma, 1 (2.3%). Among complaints we found headache (66%), giddiness (38%), decreasing of vision (25%), irritability (20%), pain in heart (20%), heartbeats (14%), disorders of sleep (11%), growth retardation (9.5%), etc.

The frequency of neuroendocrine and metabolic disorders was: revealed endocrine encéphalopathy (66%), arterial hypertension (41%), secondary hypogonadism (2%), osteopenia (20%), dislipidemia (20%), polydipsia (20%), poliuria (18%), panhypopituitarism (16%), diabetes insipidus (11%), secondary hypocorticism (9.5%), heart ishmemic disease (6.8%), osteoporosis (6.8%), erectile dysfunction (6.8%), bitemporal hemianopsiya (4.5%), nephrotisitic (4.5%), hypergonadotrop hypogonadism (2.3%), etc.

Hormonal profile showed hypogonadotropic hypogonadism in 43 patients (98%; mean LH ranged 2.5 mIU/l, FSH 3.08 mIU/l) and significantly low total testosterone levels (mean 6.24 ng/ml), free testosterone – 12.5 ng/ml, sex-steroid-coupled globuline – 36.6 nmol/l, STH – 0.56 nmol/l, IGF1 – 64.78 nmol/l, testosterone levels (mean 0.6 pg/ml respectively.

Conclusions
i) For patients with different pituitary adenomas and obesity more distinctive deficiency of STH, IGF1, and hypogonadotropic-hypogonadism (98%). ii) The risk of development of metabolic disorders is very high (WC > 104 cm).

DOI: 10.1530/endoabs.32.P670

P671
A case of idiopathic hypogonadotropic hypogonadism which attained remission by LH and FSH treatment
Yui Watanabe1,2, Takeshi Hayashi1,2, Hiroyuki Yamazaki1, Katsuyoshi Tojo1 & Kazanori Utsunomiya1,2
1Department Kawaguchi Municipal Medical Center, Saitama, Japan; 2The Jikei University School of Medicine, Tokyo, Japan.

A 17-year-old male was referred to our hospital with lack of secondary sex characteristics. His voice didn’t break and he lacked of pubes and hircus. His bilateral testicular volume was small and his sense of smell was normal. There was no varicocele or pituitary adenoma. His chromosomal study showed no aberrations. Serum levels of LH, FSH, total testosterone and free testosterone were 1.05 mIU/ml, 1.68 mIU/ml, 0.26 ng/ml and <0.6 pg/ml respectively. A repeated GnRH test revealed sluggish, but significant response of LH and FSH. In contrast, human chorionic gonadotropin (hCG) stimulation test showed normal response of testosterone. With these results, he was diagnosed as idiopathic hypogonadotropic hypogonadism (IHH).

Although there is no consensus in the first-line therapy for IHH, there are some case reports indicating that IHH patients attained remission after r-hFSH and hCG replacement. In our case, response of LH to GnRH might suggest effectiveness of this therapy.

However, because he disliked frequent injections, he chose testosterone replacement therapy instead of r-hFSH and hCG replacement. After 2 months, his body hair gradually grew and his voice changed. After 13 months, in anticipation of recovery of his own hormonal secretory capacity, r-hFSH and hCG replacement therapy was introduced instead of testosterone therapy. At 6 months
after initiation of the treatment, his serum level of total testosterone reached 7.33 ng/ml, then, he discontinued replacement therapy. Finally, his serum levels of LH, FSH and testosterone had been kept within normal range and he held sexual desire and activity.

We experienced a case in whom r-hFSH and hCG replacement therapy successfully normalized pulsatile gonadotropin secretion, serum testosterone level and sexual function. Because IHH has several variations, it is important to carefully choose a therapy depending on each case.

DOI: 10.1530/endoabs.32.P671

P672  
Risk factors associated with primary and secondary reduced libido in male patients with sexual dysfunction  
Giovanni Corona1, Giulia Rastrelli2, Emmanuelle Janin1, Linda Vignozzi2, Edoardo Mannucci2, Gianni Forti* & Mario Maggi3  
1Endocrinology Unit, Bologna, Italy; 2Sexual Medicine and Andrology Medicine, School of Sexology, University of L’Aquila, L’Aquila, Italy; 3Endocrine Abstracts

Introduction  
Hypocotile sexual desire is defined as a persistent or recurrent deficient or absent sexual fantasies or desire for sexual activity which should not be comorbid with other medical conditions or with the use of psychoactive medications. Reduced libido is a symptom referring more to a reduction in sexual drive for sexual activity. The aim of the present study is to investigate the risk factors of primary reduced libido (i.e. not associated with conditions causing loss of libido such as hypogonadism, hyperprolactinemia, psychopathology and/or psychoactive medications) or secondary reduced libido (i.e. with aforementioned conditions) in male patients with sexual dysfunction.

Methods  
A consecutive series of 3714 men (mean age 53.2 ± 12.5 years) was retrospectively studied. Patient’s reduced libido was evaluated using question #14 of SIEDY (“Did you have more or less desire to make love in the last three months?”)

Results  
Reduced libido was comorbid with erectile dysfunction, premature ejaculation and delayed ejaculation in 38, 28.2 and 50% respectively, whereas it was isolated in 51.6%. Reduced libido prevalence was substantially increased by hypogonadism, almost doubled by psychopathology and universally present in subjects with hyperprolactinemia (secondary reduced libido). Subjects with primary reduced libido are characterized by higher post-school qualification, more disturbances in domestic and dyadic relationships, and an overall healthy body (lower glycaemia and triglyceride levels). Accordingly, in patients with primary reduced libido the risk of major cardiovascular events as calculated with the Progetto Cuore algorithm was lower than in the rest of the sample. Features of hypogonadism- or psychopathology-associated reduced libido essentially reflect their underlying conditions. Comorbidity with other sexual dysfunctions did not affect the main characteristics of primary or secondary reduced libido.

Conclusions  
Primary and secondary reduced libido have different risk factors and clinical characteristics. Recognizing primary or secondary reduced libido will help clinicians to identify comorbidities and to tailor appropriate treatments.

DOI: 10.1530/endoabs.32.P672

P673  
The role of testosterone augmentation in patients with acute exacerbation of chronic obstructive pulmonary disease (COPD) in improving functional recovery and hospital stay  
Troy H K Puar & Yuan Tud Richard Chen  
Changi General Hospital, Singapore, Singapore.

Introduction  
Low testosterone levels are found in up to 50% of male patients with chronic obstructive pulmonary disease (COPD), and acute illness is associated with further suppression of the central and peripheral gonadal axis. Testosterone supplementation in chronic stable COPD patients has yielded mixed results, demonstrating increased lean body mass, and improved exercise capacity in some studies, but not others. Use of anabolic steroids during acute illness has shown benefits in selected populations, particularly major burns patients. We studied the use of testosterone augmentation in patients with acute exacerbation of COPD, in improving functional exercise capacity and recovery during their hospitalisation.

Methods  
We conducted a randomised, placebo-controlled trial in 60 consecutive patients admitted with the primary diagnosis of acute exacerbation of COPD. Patients with a secondary diagnosis of other concomitant acute illness such as myocardial infarction, or acute renal failure were excluded. At baseline, blood tests (FSH, LH, Testosterone, SHBG, Albumin, Full blood count), anthropometric measurements, BORG dyspnea scale and 6 min walk tests (6MWT) were conducted. Patients were then randomised to receive either testosterone cypionate (400 mg i.m.) or placebo on 1st day of admission. BORG dyspnea scale and 6MWT were repeated during the hospitalisation and 2 weeks after discharge. Outcome measures included duration of hospitalisation, BORG dyspnea scale and 6MWT results. Patients will be stratified by their baseline testosterone levels.

Results  
Recruitment of subjects is currently still ongoing. Currently, 10 patients have been recruited. Preliminary data analysis of the subjects (age range 62–78 years) show a trend towards a shorter hospitalisation stay, and improved dyspnea scale and 6MWT results.

Conclusion  
Testosterone supplementation may offer a novel therapy to improve recovery from acute illness, particularly in patients with COPD who often have a low baseline testosterone level.

DOI: 10.1530/endoabs.32.P673

P674  
Forty six, XX male sex reversal syndrome with infertility: a case report  
Ayse Akkurt, Pınar Sisman, Canan Ersoy, Erdinc Erturk, Ercan Tuncel & Sazi İmamoğlu  
Uludag University Medicine School, Bursa, Turkey.

Sex reversal syndrome (SRS) is a kind of human genetic disease about gender dysplasia, which is characterised by inconsistency between gonadal sexuality and chromosome sexuality. The clinical types include 46, XY female SRS and 46, XX male SRS. The early studies of human gonadal differentiation found that human Y chromosome contains testis-determining factor (TDF) found that the sex-determining region Y (SRY) gene, which is located in Y chromosome, was the best candidate gene for TDF; and confirmed that protein encoded by it played an important role in the process of sex determination. 46, XX male SRS is characterized by the presence of a 46, XX karyotype; male external genitalia ranging from normal to ambiguous; two testicles; azoospermia; and absence of Mullerian structures. Approximately 80% of individuals with 46, XX testicular DSD present after puberty with normal pubic hair and normal penile size, but small testes, gynecomastia, and infertility resulting from azoospermia. It is generally a result of unequal crossing over between X and Y chromosomes. Approximately 20% of individuals with 46, XX male SRS present at birth with ambiguous genitalia. Gender role and gender identity are reported as male. If untreated, males with 46, XX male SRS experience the consequences of testosterone deficiency.

We report a case of XX male with chief complaints of infertility. A 29-year-old infertile male was referred to the Urology Department. His height was 166 cm and weight 74 kg. He had normal external male genital phenotype and secondary sex characters. No gynecomastia was noted. At physical examination soft and atrophic testes were palpated. Laboratory analysis and testis biopsies indicated nonobstructive azoospermia. Serum concentrations of LH and FSH were elevated at 12.8 mIU/ml (normal range 1.2–8.75 mIU/ml) and 31.88 mIU/ml (normal range 1.3–13.8 mIU/ml) respectively. Testosterone hormones level was normal at 4.8 ng/ml (normal adult male range 2.8–11 ng/ml), as was the serum prolactin concentration at 9 ng/ml (normal range 1.2–29 ng/ml). Peripheral blood cultures from this phenotypically normal male showed a normal female. Chromosomal analysis showed 46, XX karyotype.

In conclusion, a multidisciplinary approach should be adopted in the management of 46, XX individuals. All patients with azoospermia must be karyotyped. Sperm donation remains the only fertility treatment available. The 46, XX patients need lifelong followup led by an endocrinologist with regular imaging of the gonads, bone density measurements, baseline blood tests, and testosterone supplementa-

Psychological support is a key part of a holistic approach.

DOI: 10.1530/endoabs.32.P674
P675

Investigation on psychological symptoms improves ANDROTEST accuracy in predicting hypogonadism in subjects with sexual dysfunction

Giusi Rastrelli1, Giovanni Corona1,2, Elisa Bandini1, Carolina Strada1, Elisa Maseroli1, Valdo Ricca1, Carlo Faravelli1, Edoardo Mannucci1 & Mario Maggi1

1University of Florence, Florence, Italy; 2Maggiore Hospital, Bologna, Italy.

The role of psychological symptoms in recognizing late-onset hypogonadism (LOH) is still controversial. The aim of the study is to evaluate the association between LOH and specific psychological symptoms and to verify whether investigating intra-psychic domain improves the accuracy of a validated case-history tool (ANDROTEST) in detecting LOH. A consecutive series of 1009 subjects (mean age 49.23 ± 13.34) consulting for sexual dysfunction was studied. Intra-psychic symptoms were investigated by Middlesex Hospital Questionnaire (MHQ), a self-reported questionnaire for screening of mental disorders. A minimum set of 2 MHQ items was identified through iterative ROC curve analysis, with assessment of sensitivity and specificity for hypogonadism (calculated free testosterone <0.225 nmol/l) in an exploratory sample of 462 patients. Sensitivity and specificity were verified in a validation sample of 547 subjects, in which the final 2-item version showed an accuracy of 58.4 ± 3.2% in detecting hypogonadism. The combination of the 2-item score with ANDROTEST increased the accuracy in predicting hypogonadism (0.741 ± 0.029; P < 0.0001), when compared to ANDROTEST (0.696 ± 0.018; P < 0.0001) and the 2-item score (P < 0.05) alone. Hence, combining these two psychological symptoms with a physical scoring system improves its ability in detecting hypogonadism. The combination of the scores should be tested in other studies.

DOI: 10.1530/endoabs.32.P675

P676

Two unconventional risk factors for major adverse cardiovascular events in subjects with sexual dysfunction: low education and reported partner’s hypoactive sexual desire in comparison with conventional risk factors

Giulia Rastrelli1, Giovanni Corona1, 2, Alessandra Daphne Fisher1, Edoardo Mannucci1 & Mario Maggi1

1University of Florence, Florence, Italy; 2Maggiore Hospital, Bologna, Italy.

Introduction

The classification of subjects as low or high cardiovascular (CV) risk is usually performed by risk engines, based upon multivariable prediction algorithms. However, their accuracy in predicting major adverse CV events (MACE) is lower in high-risk populations, since they take into account only conventional risk factors. Aim

To evaluate the accuracy of Progetto Cuore risk engine in predicting MACE in subjects with erectile dysfunction (ED), and to test the role of unconventional CV risk factors, specifically identified for ED.

Methods

A consecutive series of 1,233 men (mean age 53.33 ± 9.08 years) attending our outpatient clinic for sexual dysfunction was longitudinally studied for a mean period of 4.4 ± 2.6 years.

Main outcome measure

Several clinical, biochemical, and instrumental parameters were evaluated. Subjects were classified as high- or low-risk, according to previously reported ED-specific risk factors.

Results

In the overall population, Progetto Cuore-predicted population survival was not significantly different from the observed one (P = 0.545). Accordingly, Receiver Operating Characteristic (ROC) analysis shows that Progetto Cuore has an accuracy of 0.697 ± 0.037 (P < 0.001) in predicting MACE. Considering subjects at high-risk according to ED-specific risk factors, the observed incidence of MACE was significantly higher than the expected for both low-educated and patients reporting partner’s hypoactive sexual desire (HSD), both < 0.05, but not for other described factors. The area under ROC curves of Progetto Cuore for MACE in subjects with low-education and reported partner’s HSD was 0.659 ± 0.053 (P = 0.008) and 0.550 ± 0.076 (P = 0.570) respectively.

Conclusion

Overall, Progetto Cuore is a proper instrument for evaluating CV risk in ED subjects. However, in ED, other factors as low-education and partner’s HSD concur to risk profile. At variance with low-education, Progetto Cuore is not accurate enough to predict MACE in subjects with partner’s HSD, suggesting that the latter effect is not mediated by conventional risk factors included in the algorithm.

DOI: 10.1530/endoabs.32.P676

P677

‘It takes two to tango’: the relational domain in a cohort of subjects with erectile dysfunction (ED)

Valentina Boddi1, Giulia Rastrelli1, Giovanni Corona2, Alessandra Daphne Fisher1, Gianni Forti1 & Mario Maggi1

1Andrology Unit, Clinical Physiopathology, Florence, Italy; 2Endocrinology Unit, Bologna, Italy.

Introduction

The relational domain of erectile dysfunction (ED) is difficult to investigate in a clinical setting. We developed and validated SIEDY, a 13-item structured interview, which assesses, beside the organic (Scale1) and intra-psychic (Scale 3) domains, also the relation one (Scale 2). We previously established a pathological threshold for SIEDY Scale 1 and 3. Aim

To identify a pathological threshold of SIEDY Scale 2.

Method

A non-selected, consecutive series of 2,992 subject with ED was retrospectively evaluated. In a first consecutive series of 844 patients (Sample A, studied without systematically applying a psychometric test; Middlesex Hospital Questionnaire, MHQ) a pathological threshold of SIEDY Scale 2 score was identified through receiver operating characteristic, using, as surrogate marker of impaired couple relationship, at least a positive answer to two standard questions on conflict within the couple and on the presence of extramarital affairs.

Main outcome measure

Sensitivity and specificity, along with possible associations with biological and psychological correlates were verified in a further sample of 2,148 patients (Sample B).

Results

In sample A, a threshold of Scale 2 score ≥ 2 predicts couple impairment with a sensitivity of 53% and specificity of 66%, and an overall accuracy of 62.0 ± 2.2% (P < 0.0001). When this threshold was verified in sample B, Scale 2 score ≥ 2 was associated with a higher risk of anxiety and depressive symptoms, higher prevalence of psychopathology, and higher Scale 3 scoring, even after adjusting for confounders. In the same sample, a Scale 2 score ≥ 2 was associated with a reduced intimacy during sexual intercourse and overall worse sexual functioning.

DOI: 10.1530/endoabs.32.P677

Neuroendocrinology

P678

Genotype and phenotype characterization of the cohort of Italian patients with idiopathic central hypogonadism (ICH)

Marco Bonomi1, Domenico Vladimiro Libri1, Fabiana Guizzardi1, Paolo Dumunico1, Antonio Agostino Sinisi1, Manuela Simon1, Mohamad Magnie2, Csilla Krausz2, Luca Persani1,2 & On behalf of the Italian Societies for Endocrinology and Pediatric Endocrinology1

1Divisione di Medicina Generale ad indirizzo Endocrino-Metabolico and Laboratorio di Ricerche Endocrino-metaboliche, IRCCS Istituto Auxologico Italiano, Cusano Milanino, Milan, Italy; 2Dipartimento di Scienze Cliniche e di Comunità, Università degli studi di Milano, Milan, Italy; 3Dipartimento di Scienze Cardiovascolari e Respiratorie, II Università di Napoli, Naples, Italy; 4Dipartimento di Biomedicina, Metabolism e Scienze Neurali, Università di Modena e Reggio Emilia, Modena, Italy; 5Dipartimento di Scienze Pediatriche, IRCCS Gianna Gaslini, Università di Genova, Genova, Italy; 6Dipartimento di Fisiopatologia Clinica, Unità di Andrologia, Università di Firenze, Florence, Italy.

ICH is a rare disease characterized by a complex pathogenesis, but with a strong genetic component. ICH may be associated to several other morphogenetic or inborn defects, such as the osmic defects that identify the Kallmann syndrome (KS). The description of several pedigrees including relatives affected either with ICH or KS and with no other clinical or biochemical evidence of ICH suggests the existence of a genetic component. ICH may be associated to several other morphogenetic or inborn defects, such as the osmic defects that identify the Kallmann syndrome (KS). The description of several pedigrees including relatives affected either with ICH or KS and with no other clinical or biochemical evidence of ICH suggests the existence of a genetic component.

Endocrine Abstracts (2013) Vol 32
DHEA enhances working memory and prevents distraction: behavioural and ERP evidence from an auditory–visual distraction paradigm
Sónia Vale1,2, Lenka Selinger1, João Martin Martins2, Manuel Bicho3, Isabel Carmo2 & Carlès Escera2
1University of Barcelona, Barcelona, Catalonia, Spain; 2University of Lisbon, Lisbon, Portugal.

Introduction
Several studies suggest DHEA and DHEAS (DHEA(S)) are related to memory enhancement and a better performance under stress. An anti-cortisol action may contribute to those relations. We looked for a new level of evidence, by studying DHEA(S) and cortisol relations to working memory (WM) and distraction in humans also at the electrophysiological level.

Subjects and methods
Twenty-eight healthy female volunteers (18–26 years old) were presented a well-established auditory–visual distraction task protocol. EEG was recorded during the performance of one task with WM load (WM1) and other without, while ignoring task-irrelevant sounds (80% standard – st; 20% novel – nov). Novelty-P3 was identified in the nov minus st difference waveforms. Salivary DHEA, DHEAS and cortisol were measured before each task and at 30 and 60 min.

Results
With simultaneous WM load and distraction: i) Hit rate decrease was directly related to basal cortisol (P < 0.05) and inversely related to DHEA reaction (300 min) increase between conditions (P < 0.05); and ii) Reaction time increase was inversely related to basal cortisol (P < 0.05) and directly related to DHEA reaction increase between conditions (P < 0.005). Regarding auditory ERPs, novelty-P3 amplitude in WM1 was directly related to cortisol/DHEA ratio before that task (P = 0.007). In visual ERPs, P300 amplitude in WM1 was directly related to basal DHEAS (P = 0.011) and changed due to WM load in direct relation to DHEA reaction (P = 0.005).

Discussion
In more demanding situations, higher basal cortisol was related to faster answers and more errors whereas DHEA reaction presented opposite relations. At the electrophysiological level, distraction during WM load was in direct relation to cortisol/DHEA ratio and processing of the task-relevant visual stimulus was enhanced by higher basal DHEA and DHEA reaction. Overall, higher cortisol level was related to worse performance and more distraction while DHEA(S) showed opposite effects.

DO: 10.1530/endoabs.32.P679

P681
Hypothalamic melanin-concentrating hormone influences liver and adipose lipid metabolism
Monica Imbernón1,2, Daniel Beirou1,2, Maria J Vazquez1,2, Donald A Morgan3, Christelle Veyrat-Durebeix1, Begonha Porteiro1,2, Adenis Diaz-Arteaga1,2, Ana Sendi1,2, Omar Al-Massadi1,2, Douglas Santiago de Compostela, Spain; 2CIBER Fisiopatología de la Obesidad y Nutrición (CIBERObn), Santiago de Compostela, Spain; 3Department of Pharmacology, University of Iowa Carver College of Medicine, Iowa, USA; 4Laboratory of Metabolism, Division of Endocrinology, Diabetology and Nutrition, Department of Internal Medicine, Faculty of Medicine, Geneva, Switzerland; 5Department of Morphological Sciences, School of Medicine, Santiago de Compostela, Spain; 6Grupo Fisiopatología Endocrina, Complejo Hospitalario Universitario de Santiago- Instituto de Investigación Sanitaria (IDIS/SERGAS), Santiago de Compostela, Spain; 7Howard Hughes Medical Institute, Program in Molecular Medicine, University of Massachusetts Medical School, Worcester, Massachusetts, USA; 8Department of Vascular Biology and Inflammation, Centro Nacional de Investigaciones Cardiovasculares Carlos III, Madrid, Spain.

Introduction
Melan-in-concentrating hormone (MCH) is an orexigenic neuropeptide which is located in the lateral hypothalamus and regulate the energy balance. MCH deficient mice are hypophagic, lean and do not develop hepatosteatosis when fed on high fat diet. The MCH increases food intake and adiposity, so we sought to investigate the role of the MCH on adipocyte and hepatic metabolism.

Methods
MCH were chronically administered into the lateral ventricles of rats brain, using osmotic pumps that released the MCH for a week. To study whether the sympathetic nervous system mediates the actions of MCH on white adipose tissue, deficient mice for the three beta-adrenergic receptors were used (triple knockout mice). To determine whether the central effect of MCH on the liver was mediated through the parasympathetic nervous system (PSNS), the vagus nerve was dissected. Adenoviral particles overexpressing MCH receptors (MCH-R) were stereotaxically administered into arcuate and lateral hypothalamus (LHA, 15th European Congress of Endocrinology 2013
Several Rab proteins control secretory granule trafficking and, hence, hormone release, by regulating the activity of different components of the secretory granule transport machinery. Particularly, Rab18 inhibits secretory granule movement, which leads to reduced neuropeptide and hormone secretion in PC12 phaeochromocytoma cells and ACTH-secreting ATt20 cells, respectively, but how this GTPase accomplishes its role and the identity of the proteins that regulate Rab18 activity (effectors) remain unknown. In this work, we searched for the Rab18 effectors that ultimately determine its participation in neuroendocrine secretion. Time-lapse video-microscopy revealed that a functional microtubule-based cytoskeleton network is necessary for Rab18 to anchor to the secretory granules and to inhibit their movement. Furthermore, yeast two-hybrid experiments allowed us to identify a plethora of putative Rab18 interacting proteins, among which it is worth to highlight a subunit of the microtubule-associated molecular motor kinesin-1, for its well-known role in anterograde secretory granule transport. We confirmed Rab18/kinesin-1 interaction by Fluorescence Resonance Energy Transfer (FRET), which also showed that such an interaction only occurs with the active, GTP-bound form of Rab18. On the other hand, HITT overexpression increased Rab18 association to the surface of secretory granules in PC12 cells, which suggests that HITT could act as a guanine exchange factor (GEF) for this Rab GTPase. Altogether, our results suggest that Rab18 reduces neuroendocrine secretion by interacting and regulating the activity of various components of the microtubule-based transport apparatus.

Introduction
Quality of life in transsexual persons after transition is among the most important outcome factors.

Methods
A specialist center cross-sectional study in 193 transsexual women and 128 transsexual men (mean age 42.5 years) after on average 7.4 years of cross-sex hormone therapy and 6.6 years since sex reassignment surgery (SRS), compared to an age- and gender matched control population (1 to 3 matching). Self-reported physical and mental health using the Dutch version of the SF-12 Health survey.

Outcome factors.

Results
Compared to age-matched control men and women, transsexual women scored worse both on physical and mental functioning (all P values <0.001). Transsexual men reported equal degree of physical functioning compared to control women, but scored worse than control men. Mental well-being in transsexual men was poorer in comparison with control men and women (all P values <0.001). In the total sample, age was negatively correlated with physical functioning, whereas educational level was positively associated. Patients with the lowest income quartile had worse physical and mental functioning compared to the others. Participants who lived with a partner had a better mental well-being. In transsexual men, having children was positively associated with mental well-being. In transsexual women, physical well-being was positively associated with mental and physical functioning (both P<0.001).

Conclusion
Results of the current study indicate transsexual men and women after long-term cross-sex hormone treatment and SRS report worse mental well-being compared to a control population. QOL in transsexual persons showed a strong association with treatment satisfaction, social and economical determinants.

DOI: 10.1530/endoabs.32.P684

Roles of kisspeptin partners, NKB and dynorphin, in the control of gonadotropin secretion: revisiting the KNDy paradigm

Francisco Ruoz-Fino1,2, David García-Galán1,3, Maria Manfredi-Lozano1,2, Silvia Leon1,2, Miguel A Sanchez-Garrido1,2, Juan Roa1,3, Leonor Pinilla1,2, Victor Navarro1,5, & Manuel Tena-Sempere2,1

1Physiology Section, University of Cordoba and IMIBIC, Cordoba, Spain; 2CIBER Fisiopatologia de la Obesidad y Nutricion, Cordoba, Spain; 3Brigham and Women’s Hospital, Boston, USA.

KNDy neurons, which co-express kisspeptins, neurokinin B (NKB) and dynorphin (Dyn), play a key role in the tonic control of gonadotropin secretion by modulating the GnRH release. The assumed KNDy model proposes that NKB and Dyn (as stimulatory and inhibitory signals, respectively) auto-regulate the secretion of kisspeptins onto GnRH neurons. However, some aspects of this paradigm remain poorly defined. In this context, the aims of this work were to characterize i) the putative effects of NKB signaling in the control of FSH secretion ii) the role of Dyn tone in shaping gonadotropin secretion and responses to NK. For the first goal, the effects of NKB agonist, senktide, on FSH release were explored across rat postnatal development; LH responses to senktide and FSH responses to kisspeptin-10 (Kp-10) were also assessed. Pre-pubertal rats displayed FSH (as well as LH) responses to central injection of senktide; FSH responses to Kp-10 were also detected at this age. In clear contrast, adult females were totally irresponsive to senktide in terms of FSH release, despite their proven LH responsiveness to NKB. In turn, adult males, which are highly responsive to Kp-10, did not display FSH (or LH) responses to senktide. For the second goal, gonadotropin responses to NK stimulation were explored in adult rats after blockade of Dyn receptors (KOR) with the antagonist, nor-BNI. Adult male rats became responsive to senktide in terms of LH secretion after KOR blockade. Moreover, female rats displayed unambiguous FSH responses to senktide after treatment with nor-BNI.

In sum, we have documented i) the divergent patterns of gonadotropin (FSH vs LH) responses to NKB and Kp-10 stimulation ii) the role of Dyn signaling in inhibiting basal gonadotropin secretion and their responses to NKB. All in all, our data contribute to refine our present understanding on how different elements of the KNDy node participate in the dynamic and differential control of the secretion of both gonadotropins in both sexes and at different stages of postnatal maturation.

DOI: 10.1530/endoabs.32.P684

The small GTPase Rab18 modulates neuroendocrine secretion by interacting with components of the microtubule-based secretory granule transport machinery

Rafael Vazquez-Martinez, Farid Almahbouda, Yoana Rabanal, Alberto Diaz-Ruiz, Socorro Garcia-Navarro & Maria M Malagon

Department of Cell Biology, Physiology, and Immunology, IMIBIC/HURS, University of Cordoba, CIBERObn, Cordoba, Spain.

Rab18 is a critical small GTPase implicated in the regulation of the secretory machinery in a wide variety of cell types, including gonadotrophs. In response to hypothalamic kisspeptin (Kp) stimulation, gonadotrophs undergo a morphologic transformation, which is mediated by Rab18. In this study, we examined the interaction of Rab18 with other components of the microtubule-based secretory machinery. We confirmed Rab18 interaction with kinesin-1 by co-immunoprecipitation, suggesting a role for Rab18 in the regulation of kinesin-1 function. Furthermore, time-lapse microscopy revealed that Rab18 and kinesin-1 proteins are colocalized in secretory granules, suggesting a direct interaction. These findings highlight the importance of Rab18 in the regulation of secretory granule transport and suggest a potential role for Rab18 in the control of gonadotropin secretion.
**P685**  
Antipsychotic-induced hyperprolactinemia: clinical particulars and relation to sexual dysfunction  
Olga Yunilainen1, Elena Starostina2, Larisa Dzeranova1, Galina Kolesnikova1, Gulnara Karina1, Mykola Goncharov1 & Ivan Dedov1  
1National Research Center for Endocrinology, Moscow, Russia; 2Moscow Regional Clinical and Research Institute (MONIKI), Moscow, Russia.

Objectives  
To assess prevalence of antipsychotic-induced hyperprolactinemia (AIH) in psychiatric in-patients and to describe its clinical characteristics and association of AIH with sexual dysfunction.  

Methods  
A cross-sectional study in 143 consecutive psychiatric in-patients (F/M = 65/78), mostly with schizophrenia (93%), currently taking antipsychotics. The patients were screened for serum prolactin, sex hormones, gonadotropin levels and macroprolactin. For assessment of any sexual dysfunction, UKU side effects rating scale (UKU), Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ) were used.

Results  
Overall prevalence of AIH was 57.0% (F, 72.0%; M, 43.6%). Macroprolactin was extremely rare (one patient only, 2.0%). AIH was asymptomatic in 19% of females and in 54% of males. Hyperprolactinemic women had a higher rate of menstrual dysfunction (56 vs 14%, P = 0.006) and galactorrhea (66 vs 0%, P < 0.001), compared to normoprolactinemic. Prolactin level inversely correlated with that of estradiol (R = -0.35, P = 0.03) and correlated positively with PRSexDQ score of questions on the impact of sexual dysfunction on quality of life (R = 0.35, P = 0.02). For assessment of sexual dysfunction, males were divided into two age groups: 19–31 and 32–45 years. Hyperprolactinemic men in the younger age group had a higher UKU score of questions on increased sexual desire (P = 0.026) compared to normoprolactinemic of the same age group. In the younger, but not in the older age group, prolactin level correlated positively with UKU score in questions about reduced sexual desire (R = 0.35, P = 0.029). There were no association between AIH and weight gain and/or obesity in patients of both genders.

Conclusions  
AIH found by screening is more than 1.5-fold prevalent than that diagnosed by referral. In patients with AIH, measurement of macroprolactin is unnecessary. AIH cause menstrual disorders (oligomenorrhea and amenorrhea), galactorrhea and decreased estradiol level in females. AIH per se does not lead to weight gain and obesity. AIH is associated with sexual dysfunction in females, affecting their quality of life. AIH is associated with change of libido (increasing or reducing) in males 19–31 years old.

DOI: 10.1530/endoabs.32.P685

**P687**  
Digenic and oligogenic cases in a large cohort of idiopathic central hypogonadism (ICH) patients  
Domenico Livi1, Marco Bonomi1, Fabiana Guzzardi1, Paolo Daminuco1, Ida Piccini1, Giovanni Russo1, Andrea Garolla1, Csilla Krausz1, Mohamed Maghnie1, Giuseppe Padova2 & Luca Persani2  
1Istituto Auxologico Italiano, Cusano Milanino, Italy; 2Università statale degli studi di Milano, Milano, Italy.

Objectives  
ICH is a rare and heterogeneous condition due to defects in the oogenesis, migration and action of GnRH secreting neurons. Recent publications indicate that ICH, though characterized by a strong genetic component, is a disease of multifactorial origin. Indeed, digenic and oligogenic defects have been described as a possible pathogenic explanation for this disease. Among the cohort of 315 ICH patients we identified 3 KS and 7 nICH patients (7 males, 3 females) with a biallelic defect. These digenic defects were quite heterogeneous involving elements on different pathways. First, a familial case (brother and sister) present a compound heterozygosity on the same gene, the GnRH2, the second pedigree show a duplication in KAL1 and a variant in FGFR1, while the other 7 show biallelic variant on different genes: PROKR2 and GnRHR; PROKR2 and FGF8, FGF8 and FGFR1 and PROKR2 in 3 cases. In this small group of patients, we observe a suggestive enrichment for complex phenotypes, such as mono or bilateral cryptorchidism, midline defects and synkinesis. One case, with PROKR2/PROKR2 variants, showed a permanent reversal of the ICH after 6 years of testosterone replacement therapy. Putting together the genetic and phenotypic data we could observed a more severe phenotype in patients carrying a biallelic defect involving the FGFR1 gene. Five out of ten patients were presenting a genetic variation on PROKR2 or FGKR1 gene suggesting that single heterozygous mutations in those genes might represent frequent causes of genetic susceptibility to ICH which would need another hit to become manifest. Finally, mutations on GnRH2 gene appear interestingly associated with the less severe phenotypes.

DOI: 10.1530/endoabs.32.P687

**P686**  
Low carbohydrate/high fat energy intake decreases estrogen receptor alpha expression in the arcuate nucleus of the rat hypothalamus  
Ayse Zengin, Maximilian Bielobudy, Amnon Horngacher, Sarina Meurer & Martin Bidlingmaier  
Ludwig Maximilians University, Munich, Germany.

Low-carbohydrate/high fat diets (LC-HFD) effectively induce body weight loss in both animals and humans; however, in rats this is paralleled by increased visceral adiposity contributing to impaired glucose tolerance. Estrogen inhibits adipose tissue accumulation, with estrogen deficient female animals displaying increased body weight and visceral adiposity with reduced insulin sensitivity, which can be reversed with estrogen replacement. Consistent with the effects seen in females, estrogen supplementation also improves insulin sensitivity in male animals. Within the hypothalamus, the arcuate nucleus (ARC) is a key area of metabolic control. To test the hypothesis that central estrogen signalling plays a role for the phenotype observed with LC-HFD in rats, we investigated whether pair-feeding is isocaloric amounts of two different LC-HFD affects estrogen receptor alpha (ERα) expression in the ARC. Male Wistar rats (12-week old) were isenergetically pair-fed on chow (CH), ‘Atkins-style’ LC-HFD1, (protein matched to chow, 78/19/1,2/2), and ketogenic LC-HFD2 (low protein content, 9/67/19/1,2/2); % of original energy (carbohydrate for) 4 weeks. Rats were perfused with 4% paraformaldehyde and excised brains were cryosectioned at 30 μm and immunohistochemistry was used to visualize ERα expression. Overall, ERα was selectively expressed in the ARC. When comparing the different diet groups, immunohistochemistry revealed a decreased expression of ERα in the ARC of both LC-HFD1 and LC-HFD2 when compared to CH rats. There was no difference between LC-HFD1 and LC-HFD2. In conclusion, due to the fundamental role of estrogen in the control of adiposity and insulin sensitivity, our findings suggest that central expression of ERα is regulated by the macronutrient composition of a diet. Furthermore, the phenotype observed with LC-HFD may be related to decreased ERα expression in the ARC.

DOI: 10.1530/endoabs.32.P686

**P688**  
The characterization of sleep–wake pattern and its association with melatonin, as a marker of the circadian function of the suprachiasmatic nucleus, in craniopharyngioma patients  
Line Pickering Jakobsen1, Poul Jenumm2, Steen Gammeltoft3, Line Zachariae4, Line Rasmussen2, Søren Bjerre3, Ulla Feldt-Rasmussen2 & Marianne Klose1  
1Department of Endocrinology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; 2Danish Center for Sleep Medicine, Copenhagen University Hospital, Glostrup Hospital, Glostrup, Denmark; 3Department of Clinical Biochemistry, Copenhagen University Hospital, Glostrup Hospital, Glostrup, Denmark.

Hypothesis  
We hypothesised that damage to the hypothalamus by local tumour, surgical treatment, or irradiation might involve the suprachiasmatic nucleus and thereby melatonin secretion, leading to disturbed circadian function and clinical manifestations such as daytime sleepiness and fatigue in craniopharyngioma patients.

Objective  
We aimed to assess the influence of craniopharyngiomas and their treatment on melatonin secretion, sleep pattern, sleep quality, fatigue, and sleepiness.

Subjects and measures  
We included 15 patients with craniopharyngioma and 15 gender, age, and BMI matched healthy controls. Salivary melatonin and cortisol were measured over a 24 h-period. Sleep–wake patterns were characterized by two weeks of actigraphy recordings and sleep diaries. Sleepiness, fatigue, sleep quality, and general health were assessed by the following questionnaires: i) ‘Multidimensional Fatigue Inventory’; ii) ‘Pittsburgh Sleep Quality Index’; iii) Epworth Sleepiness Score; and iv) ‘Short Form-36’.

Results  
The patients had lower general health (P = 0.01), increased mental fatigue (P = 0.05), increased daytime dysfunction (P = 0.05), increased sleep latency (P = 0.04),
and tended to have increased daytime sleepiness, general fatigue, and impaired sleep quality compared to healthy controls (all $P \leq 0.08$). Patients had lower AUC-melatonin ($P = 0.04$) and higher evening cortisol concentrations. Low midnight melatonin was associated with reduced sleep time ($P = 0.03$) and efficiency ($P = 0.02$), and borderline to increased sleepiness, impaired sleep quality, and physical health ($P \leq 0.08$). High midnight cortisol levels were associated with an increased number of awakenings ($P = 0.02$) and sleep time ($P = 0.07$). Midnight melatonin remained independently related to sleep time after adjustment for cortisol.

Conclusions
Our data indicated a relationship between low midnight melatonin and reduced sleep time, impaired sleep efficiency, and reduced physical activity in craniopharyngioma patients. This might be due to the influence of craniopharyngioma on the sleep regulatory nuclei.

DOI: 10.1530/endoabs.32.P688

P689
Pituitary adenoma and associated tumors
Sandra Pekic Djurdjevic1,2, Ivan Soldatovic1,3, Mirjana Doknic1,2, Dragana Miljic1,4, Marko Stojanovic2 & Vera Popovic2,4
1Faculty of Medicine, University of Belgrade, Belgrade, Serbia; 2Clinic of Pituitary adenoma and associated tumors, Center Belgrade, Belgrade, Serbia; 3Institute of Medical Statistics and Informatics, Belgrade, Serbia.

Results
Thirty-four percent of NFPA patients and 27% of acromegals had the first-degree relative(s) with cancer, significantly higher than patients with prolactinoma, 9/158). Eighteen of these PA patients diagnosed with cancer and their family history of malignancy, shows that 39/485 patients with PA had a family member affected with cancer of any type (acromegaly, 13/121; NFPA, 17/206; prolactinoma, 11/158) from the period 2000–2012. Results Fifty percent of patients with PA had a family member affected with cancer. Thirty-four percent of NFPA patients and 27% of acromegals had the first-degree relative(s) with cancer, significantly higher than patients with prolactinoma (19%; $P < 0.006$). On the contrary, 41% of patients with prolactinoma had the second-degree relative(s) with cancer, significantly higher than patients with NFPA or acromegaly (23 and 25% of patients, respectively; $P < 0.0001$). According to PA type, 16% of patients with prolactinoma had a family member with breast cancer, significantly higher than patients with NFPA (11%) or acromegaly (7%; $P < 0.05$). 11% of patients with prolactinoma had a family member with colorectal cancer, significantly higher than patients with NFPA (6%) or acromegaly (4%; $P < 0.05$). Separate analysis of PA patients diagnosed with cancer and their family history of malignancy, shows that 39/485 PA patients had cancer of any type (acromegaly, 13/121; NFPA, 17/206; prolactinoma, 9/158). Eighteen of these PA patients diagnosed with cancer had a strong family history of malignancy, particularly NFPA patients (NFPA, n = 11; acromegaly, n = 2; prolactinoma, n = 2; $P < 0.05$). Twenty-one PA patients diagnosed with cancer did not have a family history of malignancy (NFPA, n = 3; acromegaly, n = 11; prolactinoma, n = 7).

Conclusions
i) The results suggest presence of associated tumors in families of patients with PA (in 50%); ii) There is a strong association of prolactinoma with breast and colorectal cancers diagnosed in their families; iii) 46% of PA patients who were diagnosed with cancer had a strong family history of malignancy, in particular those with NFPA.

DOI: 10.1530/endoabs.32.P689

P691
The reproductve endocrine complications of antiepileptic drugs at woman's epilepsy
Galina Odintsova1, Nadezda Koroleva1, Ludmila Saykova1,2 & Anastasia Chugunova1
1Institute of human brain of RAS, Saint Petrsburg, Russia; 2NWSMU n.i.i.Mechnikov, Saint Petrsburg, Russia.

Purpose
To study reproductive endocrine complications (REC) of antiepileptic drugs (AEDs) at woman epilepsy.

Materials and methods
One hundred and fifty five women at the age of 16–45 years were included in prospective observational uncontrolled comparative study of the antiepileptic drugs reproductive side effects. Three groups were divided: 1 gr., monotherapy AEDs; 2 gr., polytherapy; 3 gr., no AEDs used. REC lasted more than 6 months were accounted. The diagnosis was established based on comprehensive exam, in accordance with ICD-10. Naranja algorithm was used to determine reliability of communication ‘AEDs – REC’.

Results
70 patients (45%) were in 1 gr., 65 (42%) – in 2 gr., 20 (13%) – in 3 gr. 73 patients (47%) were healthy in a total cohort. The overall incidence of REC were 53%, 75% of them due to side effects of AEDs. Comorbid REC was observed in 21 women (13%). In 61 (40%) cases were identified REC due to treatment of AEDs. REC were associated with the taking AEDs in 21 women (30%) at the 1 gr., 40 (57%) patients were healthy. In the 2 gr. REC associated with exposure to AEDs was diagnosed in 38 patients (59%). Only 2 people (10%) retained menstrual irregularities arising from preceding antiepileptic therapy in the three control gr. Differences in the frequency of REC in the comparison groups were statistically significant ($P < 0.001$). Disturbances of a menstrual cycle were determined at 57%, the amenorrhea – 10%, sterility – 10%, a syndrome of polycystic ovaries –7%, dysfunctional uterine bleedings – 3%, a delay of sexual development – 2%, a premenstrual syndrome – 11%. Differences in the frequency of disturbances of a menstrual cycle in the comparison groups were statistically significant above at polytherapy ($P < 0.001$).

Conclusion
Reproductive disturbances are a frequent side effect of antiepileptic drugs at woman epilepsy above at polytherapy. It is necessary monitoring a condition of reproductive health during treatment by antiepileptic drugs.

DOI: 10.1530/endoabs.32.P691
DHEA and cortisol response to working memory
Sónia Vale1,2, Lenka Selinger1, João Martin Martins2, Ana Gomes2, Manuel Bicho1, Isabel Carmo1 & Carles Escera1
1University of Barcelona, Barcelona, Catalonia, Spain; 2University of Lisbon, Lisbon, Portugal.

Introduction
Several studies reported DHEA relations to memory and cognition improvement. An anti-cortisol action may contribute to those relations. The effect of working memory (WM) on DHEA levels is unknown. We studied DHEA and cortisol reactivity in humans after a WM stimulus with simultaneous distraction.

Subjects and methods
Twenty eight healthy female volunteers (18–26 years old) were presented a well-established auditory–visual distraction task protocol. Subjects performed one task with working memory (WM) load (WM1) and other without (WM0), 120 min apart, with counterbalanced order across subjects. Each task consisted of 500 trials (15 min), all composed by a task irrelevant sound (80% standard; 20% novel) followed by the visual stimulus that the subject had to classify. Salivary DHEA and cortisol were measured before each task (0 min) and at 30 and 60 min.

Results
DHEA raised after the second task (P = 0.016), more with WM1 load (190 ± 83 at 0 min vs 290 ± 206 pg/ml at 30 min, P = 0.045) and cortisol declined after WM0, when it was the first task (1290 pg/ml at 0 min vs 930 pg/ml at 30 min vs 620 pg/ml at 60 min, P < 0.05) so that DHEA and cortisol levels were higher when WM1 was the second task (DHEA: P = 0.022, cortisol: P = 0.004). Cortisol:DHEA ratio was lower in the second task (P = 0.001) and decreased after both tasks performance (P = 0.036).

Discussion
Under distraction, higher DHEA levels were found after the performance of two consecutive cognitive tasks. DHEA raised and cortisol did not decline after WM load when it was the second task, suggesting that consecutive cognitive tasks and WM load may raise DHEA and prevent cortisol decrease. DHEA increase with WM load contributed to lower cortisol:DHEA ratio after that task. Previous studies related higher DHEA levels with memory enhancement. The present results suggest that cognitive tasks and WM load may also be a stimulus against DHEA decay.

DOI: 10.1530/endoabs.32.P692

Neuroprotective effects of estrogen rely on neuroglobin upregulation
Marco Fiocchetti, Paolo Ascenzi & Maria Marino
Section Biomedical Science and Technologies, TRE Department of Science, University Roma, Rome, Italy.

Estrogens, in particular 17β-estradiol (E2), orchestrate cellular mechanisms involved in the development and differentiation of various neuron populations, modulation of synaptic plasticity, induction of neuronal survival, and neurogenesis. Beneficial effects of E2 have been widely reported against a variety of insults, including H2O2 injury, serum deprivation, and glutamate excitotoxicity. Recently, we identified E2 as an endogenous modulator of a new neuroprotectant protein, neuroglobin (Ngb). Here, our principal aim is to identify the molecular mechanisms of neuroglobin up-regulation by estrogen and how it contributes to estrogen neuroprotection.

Results
E2 increased Ngb expression and protein levels in vivo and in vitro. Ngb is a homologue of the globin family with a neuroprotective role in several pathologies. Ngb relocalizes mainly into mitochondria where the physical association with the mitochondrial cytochrome c oxidase complex reduces its release into the cytosol. As a consequence, a decrease of caspase-3 activation and, in turn, of the apoptotic cascade activation takes place. Ngb induces Ngb level regulation also in astrocytes, where this globin is required for E2 effects in preventing lipopolysaccharide (LPS)-induced cytochrome release. All these effects are mediated by estrogen receptor β (ERβ) via genomic and extranuclear signals involving p38/ERK5/MAPK pathway. As a whole, the well known neuroprotective effects elicited by E2 may, at least in part, be explained by an enhanced Ngb expression in neurons and astrocytes. The principal role played by Ngb in the brain could be related to the reduction of neuronal death by resetting the trigger level of apoptosis and inhibition of pro-inflammatory cytokines expression, leading to the onset of physiological response to stress. E2 acts to accelerate Ngb neuroprotective effect rapidly enhancing its levels in both neurons and astrocytes.

DOI: 10.1530/endoabs.32.P693

Diagnosis and management of patients presenting hyponatremia while receiving parenteral nutrition
Emilia Gomez Hoyos, Martin Cuesta Hernandez, Francisco Fernandez Capel, Teresa Vidal, Maria Del Pilar Matia Martin, Lucio Cabrerizo Garcia, Miguel Angel Rubio Herrera, Natalia Perez Ferre, Alfonso Calle Pascual & Isabelle Runkle De La Vega
Hospital Clinico San Carlos, Madrid, Spain.

Introduction
Hyponatremia is the most frequent electrolyte alteration in hospitalized patients, and is associated with increased morbimortality. Hyponatremia in patients receiving parenteral nutrition (PN) is generally overlooked. Our objective was to classify the types of hyponatremia observed in patients on PN, and to describe the prescribed treatments and evaluation.

Material and methods
We undertook a prospective study of all patients on medical wards receiving PN with hyponatremia – serum sodium (SNa) < 135 mmol/l – attended by our team between 01/06/12 and 01/12/12. Study included physical examination, serum (S)/plasma (P) and urine(P) electrolytes and osmolality (Osm), glycemia, circulating TSH, fT3, cortisol, ACTH, urea/creatinina, and transaminase levels.

Results
Twenty out of 85 patients (23.5%) presented hyponatremia (9 women), average age 68.5 (s.d. 13.15), SNa 130.8 mmol/l (s.d. 4.03), nadir SNa 128.95 (s.d. 3.2), 70% (14) were euvolemic, 20% (4) hypovolemic, and 10% (2) hypervolemic. SNa euvolemic: 130.5 (IR 129–133), PNa 274 mOsm/Kg (IR 266.7–280). SNa hypovolemic: 121 mmol/l (IR 82–128), Osm 454 mOsm/Kg (IR 366–780).

Discussion
Three cases of pain-related physiologic ADH elevation were treated with analgesics: SNa pre-treatment 132.5 (IR 131.6–137.6) and post-treatment 137.5 (IR 133–138). 10 cases presented SIADH. Of whom 8 received fluid restriction and increased sodium in PN: SNa pre-treatment 129 (IR 129–133) post-treatment 134.0 (IR 133.2–136.1), 2 required tolvaptan: SNa pre-treatment 127.83 (IR 126.6–129) post-treatment 137 (IR 136–138); In one case of thiazide-induced hyponatremia the diuretic was discontinued: SNa pre-withdrawal 133, post-withdrawal 137. Hypovolemic were treated with an increase in PN volume. SNa pre-treatment 132 (IR 124.2–137.7), post-treatment 134 (IR 132.1–136.5). HYPERVOLEMICS received furosemide and NP volume was reduced: SNa pre-treatment 130.50 (IR 130.0–131.0), post-treatment 137.5 (IR 133–142).

Conclusions
SIADH was the most frequent cause of hyponatremia in our PN-treated patients. A correct diagnosis of the cause of hyponatremia in patients receiving PN is essential for adequate treatment of this common electrolyte disorder.

DOI: 10.1530/endoabs.32.P694

Des-acyl ghrelin acts directly and independently and counteracts acyl-ghrelin-induced neuronal activity in the central melanocortin system of rats
Darko Stevanovic1,2, Patric Delhanty1, Axel Themmen1, Vera Popovic1, Joan Holstege1 & Aart-Jan van der Lely1
1Department of Medicine, Erasmus University MC, Rotterdam, The Netherlands; 2School of Medicine, Institute of Physiology, University of Belgrade, Belgrade, Serbia; 3Department of Neuroscience, Erasmus University MC, Rotterdam, The Netherlands; School of Medicine, Institute of Endocrinology, Diabetes and Diseases of Metabolism, University of Belgrade, Belgrade, Serbia.

Ghrelin, the endogenous GH secretagogue, has an important role in metabolic homeostasis. It exists in two major molecular forms: acylated (AG) and des-acylated (DAG). Many studies suggest different roles for these two forms in energy balance regulation. In the present study, we compared the effects of acute intracerebroventricular (ICV) administration of AG, DAG and their combination (AG+DAG) to young adult Wistar rats on food intake and central melanocortin system modulation. The results showed that ICV DAG did not affect food intake when compared to saline-treated rats. This treatment significantly increased the number of c-fos (marker of neuronal activity) positive neurons in the arcuate (ARC), paraventricular (PVN) and solitary tract (NTS) nuclei, while DAG suppressed AG-induced neuronal activity in PVN and NTS, 2 h postinjection. Central DAG increased melanocortin-4 (MC4R) and decreased melanocortin-3 receptor (MC3R), agouti-related protein (AgRP) and proopiomelanocortin (POMC) hypothalamic gene expressions, 5 h postinjection. These results demonstrate that DAG acts directly, centrally and AG-independently to increase neuronal activity in the melanocortin system in rats and is able to counteract AG

DOI: 10.1530/endoabs.32.P695
actions in hypothalamic PVN and NTS in the brainstem. Together with the absence of the effect on energy intake, these results indicate that DAG could affect energy homeostasis by modulation of energy expenditure via central melanocortin system.

P696 Evaluation of the efficacy of midnight salivary cortisol plus dexamethasone suppression test as screening for the diagnosis of hypercortisolism within an at-risk population

Alfonso Leal-Cerro1, Ainara Madrazo-Atutxa1, Juan Garcia-Arnes1, Cristina Lamas-Oliveira1, Mauro Boronat-Cort1, Juan A Lillo1, Carmen Fajardo1, Eulalia Urgell-Rull2, Javier Salvador1, Isabel Salinas1, Ignacio Bernabé1, Concha Paramo1, Susan Webb2, Elena Torres-Vela1, Angel Diaz2, Javier Alber1 & Antonio Leon-Justel1

1Department of Endocrinology and Nutrition. Instituto de Biomedicina de Sevilla (IBIS), Virgen del Rocio University Hospital, Seville, Spain; 2Department of Clinical Biochemistry, Barcelona, Spain.

Introduction

Endogenous Cushing’s syndrome (CS) is a rare, underdiagnosed and severe disease that carries high morbidity and mortality. Delays in treatment initiation reduce reversibility of symptoms and increase mortality rate. Current gold standard for screening, 24 h urine free cortisol, has a low reproducibility and specificity, and sampling is complicated. Midnight salivary cortisol (MSVC) determination is considered an easy and cheap test. We intend to assess its feasibility combined with suppression test to screen CS. This initiative has been developed by the Cushing’s disease (CD) working group, member of the Sociedad Española de Endocrinología y Nutrición (SEEN) and supported by Novartis.

Methods/design

Epidemiological cross-sectional study to assess MSVC plus suppression test. Secondary objectives are to describe the prevalence of CS and CD in the studied population. Patients will be performed the two tests, results from both, clinical characteristics and final diagnosis of CS or CD will be recorded.

Results

This project, named CRISAbado en SALiva De Alteraciones del cortisol (CRISALDA) was initiated on November 2012, with 13 participating sites across Spain. Sample size will be 609 patients and results from an interim analysis are expected on April 2013. Study population includes a group of patients considered at risk of presenting high cortisol levels, presenting at least 2 of the following symptoms: obesity (BMI >30), hard to control hypertension (SBP >140 and DBP >90 mmHg, >2 drugs), poorly controlled diabetes (HbA1c >7.0%), severe osteoporosis (~2.5 s.d. in T-score) or virilization syndrome. Exclusion criteria: pregnancy, age >70 years, glucocorticoid treatment, CS or CD diagnosis. Characteristics and final diagnosis of a rare disease (CD).

P697 Impact of long acting somatostatin analogs vs successful surgery on glucose metabolism in Cretan acromegalic patients

Vasili Di Raki1, Christyanna Konstantinidou1, Evgenia Karipidou1, Fotis Spyrou1, Eleftheri Vamanaki1, Evangelia Mamalaki1 & Stathis Papavasiliou1

Clinic of Endocrinology, Diabetes and Metabolic Diseases, University Hospital of Crete, Heraklion, Greece.

Introduction

Acromegaly is associated with increased cardiovascular morbidity and mortality, in part, as a consequence of the increased insulin resistance that frequently accompanies GH hypersecretion. Glucose tolerance may worsen in patients treated with somatostatin analogs (SSA).

Objective

To compare the long term effects of SSA treatment to successful surgery on glucose metabolism in Cretan acromegalic patients.

Design and methods

This is a cross-sectional study. We studied 22 normoglycemic acromegalics (12 female/10 male, age 53 ± 14). Fifteen patients were on SSA treatment (seven were controlled) and seven patients were surgically cured. The median period of SSA treatment was 10 years. Twenty seven age-and sex-matched healthy subjects were studied as controls. Glucose homeostasis was studied using the indexes stated below, at baseline and following an oral glucose challenge (OGTT 75 g). The areas under the response curves of glucose (AUCGLUC) and insulin (AUCINS) during OGTT were estimated.

Results

On average, both groups of acromegalics patients had significantly elevated fasting glucose, compared to controls (PSSA not controlled<0.01, PSSA controlled<0.001). AUCGLUC after OGTT was significantly elevated in all SSA-treated patients (PSSA not controlled=0.04, PSSA controlled=0.003). AUCINS was significantly decreased only in controlled SSA-treated acromegalics (P=0.035). No significant differences in AUCGLUC or AUCINS were observed between surgically cured acromegalics and the control group. Basal insulin secretion evaluated by HOMA-IR, % was significantly decreased in all SSA-treated patients compared to controls (P=0.001) but no difference was observed in basal and OGTT-derived insulin resistance evaluated by HOMA-IR, QUICKI and ISIComposite between acromegalics and controls.

Conclusion

Cretan acromegalics, even if cured had elevated fasting plasma glucose. SSA treatment resulted in higher glucose values in the fasting state and after OGTT, because of impaired insulin secretion, but had no impact on insulin resistance.

DOI: 10.1530/endoabs.32.P697

P698 Prevalence and causes of hyponatremia in patients with endocrine disorders

Ekaterina Pigarova1, Elena Cherepanova1,2 & Larisa Dzieranova1

1Endocrinology Research Centre, Moscow, Russia; 2Lomonosov Moscow State University, Moscow, Russia.

Objectives

To study the prevalence and causes of hyponatremia in patients with various endocrine diseases.

Methods

We had retrospectively analyzed the results of biochemical laboratory studies performed during one calendar month at the tertiary care clinic for endocrinology patients for the variations in the serum sodium concentrations. Blood sodium levels <135 mmol/l were considered as hyponatremia. For all patients with hyponatremia addition data including demographics, clinical diagnosis of primary and comorbid conditions, physical and instrumental examination records, duration of hospitalization were accessed through electronic patient’s chart.

Results

During this period a total of 1511 studies of serum sodium were performed, including hyponatremia was observed in 1.0% of patients (15/1511, 3 men/12 women). Hyponatremia occurred four times more frequently in hospitalized patients than those undergoing outpatient examination/treatment – 0.8 vs 0.2% respectively. The average age of patients with hyponatremia was 48.6 years (0.75, 85). Length of hospital stay among patients with hyponatremia on average was 26.5 days, with two patients were observed in the out-patient conditions, length of stay remaining patients ranged from 6 to 116 days. Development of hyponatremia was multifactorial and the causes included: use of diuretics – 46.7% of cases, exacerbation of adrenal insufficiency – 40%, nephropathy in type 2 diabetes mellitus – 20%, redistributional hyponatremia in decompensated type 1 diabetes mellitus due to hyperglycaemia – 6.7%, loss of sodium through the post-operative drainage from the abdominal cavity – 6.7%, acute urinary infection – 6.7%.

Conclusion

The overall prevalence of hyponatremia in patients with endocrine disorders is about 1%. Pathogenesis of hyponatremia in most cases multifactorial and most often associated with the use of diuretics, presence hypocorticism and renal disease.

DOI: 10.1530/endoabs.32.P698
**Introduction**

Obestatin has been proposed to have anorexigenic and anti-ghrelin action. An association has been found between ghrelin and its decline with ageing and muscle strength and functional capacity, probably mediated by GH–IGF1 axis. However, no information is available in relation to the role of obestatin in muscle strength and functional capacity.

**Objective**

The objective was to study obestatin concentrations in relation to handgrip strength, functional capacity and cognitive state in old women.

**Methods/design**

Prospective study; 110 women (age: 76.93 ± 6.32 years) from the Mataró Ageing Study were included. Individuals were characterized by anthropometric variables, grip strength, Barthel and assessment of cognitive impairment (Mini-Cognitive Examination (MCE), Spanish version), depressive status by the geriatric depression scale (GDS) and frailty by Fried criteria. Obestatin was measured by IRMA.

**Results**

Obestatin was negatively correlated to handgrip at basal time-point (r = 0.220, P = 0.023) and at two years follow-up (r = 0.344, P = 0.002). Obestatin divided into quartiles, showed a negative linear association with handgrip: 11.03±4.88 kg in 1st quartile, 8.75±4.08 kg in 2nd, 8.11±3.66 kg in 3rd and 7.61±4.08 kg in 4th quartile (P = 0.018). Higher obestatin levels were associated to weakness (categorized by handgrip of frailty criteria): 2.24±0.42 ng/ml in weak vs 1.87±0.57 ng/ml in non-weak; P = 0.01). Relative decrease in MCE at two year follow-up was significantly higher in individuals in the 4th quartile of obestatin in comparison with individuals in the 1st quartile (7.25±12.03% in 4th quartile vs −0.09±10.48% in 1st quartile; P = 0.064). In addition, relative decrease in Barthel score was significantly higher in individuals in the 4th quartile of obestatin in comparison with individuals in the 1st quartile (3.77±5.77% in 4th quartile vs 0.46±3.19% in 1st quartile; P = 0.019).

**Conclusions**

Obestatin is associated to low muscle strength, impaired functional and cognitive capacity in old women participating in the Mataró Ageing Study.

**DOI:** 10.1530/endoabs.32.P701

---

**Copeptin for subtype differentiation of abnormal vasopressin release in SIADH: reclassification and characterization of a novel subtype**

Wiebke Fenske1, Anna Hörning1, Jessica Sime1, Mirjam Christ-Crain2, Gabor Szinnai3, Jonas Rutishauser1, Stefan Stöck4 & Bruno Allolio1

1Endocrine and Diabetes Unit, University Hospital of Würzburg, Würzburg, Germany; 2Division of Endocrinology, University Hospitals Basel, Switzerland; 3Clinic for Internal Medicine, Hospital Center, Biel-Bienne, Switzerland; 4Department of Internal Medicine I, Center of Cardiovascular Medicine, University Hospital Würzburg, Würzburg, Germany.

**Introduction**

The syndrome of inappropriate antidiuresis (SIADH) is the most common cause of hypoosmolality. Ectopic AVP hypersecretion has long been considered as the primary mechanism of SIADH. But different types of osmoregulatory defect in AVP release have been described in this disorder. A comprehensive characterization of these different forms of SIADH in a large cohort of patients may provide important new insights into the still incompletely understood pathophysiology of SIADH, as well as the variable need for therapeutic management in SIADH.

**Methods and design**

Differences in pathological AVP osmoregulation in SIADH were characterized by serial measurement of plasma copeptin, a reliable AVP surrogate marker, in 50 patients with SIADH during osmotic stimulation. The physiological relationship between plasma copeptin and osmolality was defined by means of 68 healthy controls, who underwent the same protocol of osmotic stimulation.

**Results**

In healthy subjects, a close correlation was found between plasma copeptin and osmolality with an osmotic threshold of 282 ± 4.3 mosmol/kg H2O. In SIADH, five different types of defective AVP osmoregulation were found: 10% of patients showed a markedly elevated and osmotically-independent form of copeptin release (type A); 14% demonstrated a linear osmotic response to rising serum osmolality, but with an abnormally low osmotic-threshold (type B); 44% revealed a fixed, plateau-like copeptin secretion (type C); and 12% of patients had an AVP-independent SIADH with undetectable copeptin levels. A different, new type of SIADH was found in 20% of patients, demonstrating an inverse relation of decreasing plasma copeptin levels to increasing osmolality (type E).
Conclusion
These findings confirm the concept of ectopic AVP secretion (type A) and AVP-independent antidiuresis (type D) as osmofeedback subtypes of SIAHD. But the main pathological alteration in patients with SIAHD was the profound impairment of AVP osmoregulation well into the normosmotic range. Moreover, firstly a novel subtype of SIAHD could be described, presumably related to impaired nonosmotic inhibitory pathways in combination with altered osmoregulatory function.

DOI: 10.1530/endoabs.32.P702

P703
Neurodegenerative and inflammatory biomarkers in cerebrospinal fluid in patients with Cushings syndrome
Oskar Ragnarsson1, Peter Berglund2, Detek N Eder3, Henrik Zetterberg2, Max A Hietala4,2, Kai Blevins1 & Gudmundur Johannsson1
1Institute of Medicine at Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; 2Institute of Neuroscience and Physiology at Sahlgrenska Academy, University of Gothenburg, Göteborg, Sweden; 3Vigilance and Neurocognition Laboratory at Sahlgrenska Academy, University of Gothenburg, Göteborg, Sweden.

Background
Patients with Cushing’s syndrome (CS) in long-term remission have impaired cognitive function. Cerebrospinal fluid (CSF) biomarkers are important diagnostic tools in the work-up of patients with cognitive impairment. The aim of this study was to analyze biological markers in CSF from patients with CS in remission. Owing to the overlapping similarities between patients with CS and dementia, i.e. cognitive dysfunction and hypercorticosilaemia, the main hypothesis was that the pattern of CSF biomarkers in CS patients resembles the pattern found in other neurodegenerative disorders.

Patients and methods
This was a cross-sectional, case-controlled, single centre study. Twelve women previously treated for CS, six matched controls (age and educational level) and three women with active CS were studied. The following neurodegenerative CSF markers: total z, hyperphosphorylated z, amyloid apoptosis peptides (Aβ1–42, Aβ38, Aβ40 and Aβ42), soluble amyloid precursor protein z and β, neurofilament light proteins, glial fibrillary acidic protein and monocyte chemotactant protein 1, and inflammatory CSF markers: interferon-gamma, interleukin 1β (IL1β), IL2, IL4, IL6, IL10, II12p70, II13 and tumour necrosis factor z were analysed.

Results
The mean age (mean ± SD) was similar in patients with CS in remission (44.9 ± 14 years) and controls (42.3 ± 15.7 years; P=0.726). No differences were seen in concentrations of any neurodegenerative biomarkers between either patients with CS and remission or controls and between patients with active CS and controls. Nor was the concentration of inflammatory biomarkers different between the groups, except for IL8 which was significantly higher in patients with active CS compared to controls.

Conclusions
The pattern of neurodegenerative and inflammatory biomarkers in CSF from patients with CS does not differ from healthy controls. The underlying mechanisms of the cognitive deficits in CS are different from those seen in concentrations of any neurodegenerative biomarkers between either groups, except for IL8 which was significantly higher in patients with active CS compared to controls.

DOI: 10.1530/endoabs.32.P703

P04
Evaluation of GH deficiency and central adrenal insufficiency in patients following craniospinal irradiation in young ages: comparison between the glucagon stimulation test and the insulin tolerance test
Alla Yudina1, Tatiana Tsolovnikova1, Maria Pavlova1 & Nadezhda Mazerkina1,2
1First Moscow State Medical University n.a. I.M. Sechenov, Moscow, Russian Federation; 2Department of Endocrinology, Burdenko Neurosurgery Institute, Moscow, Russian Federation.

Methods
Thirteen patients were examined (five girls, eight boys, median age, 19 years (17; 22)). All had posterior fossa tumors in history. Median age at the time of treatment was 13 years (8; 14). Median follow-up was 5 years (3; 6). All patients received resection of the tumor, chemotherapy and CSI (35 Gy for whole brain, 55 Gy for tumor area and 32 Gy for spine). All of them performed ITT and GST. Severe GHD was diagnosed when GH was <3 ng/ml, cortisol cut-off for normal response was level 550 nmol/l.

Results
9/13 patients diagnosed severe GHD (median GH, 0.89 ng/ml (0.6–1.4)) in GST and 12/13 patients revealed GHD (median GH, 0.85 ng/ml (0.37–1.65)) in the ITT. 9/13 patients had CAI in GST (median peak plasma cortisol, 385 nmol/l (335; 476)). But the diagnosis was refuted in 49 patients in ITT, peak plasma cortisol in this was >550 nmol/ml (Me 645 nmol/l (624–676)).

Conclusions
The obtained results allow us to recommend GST as initial outpatient test. If patient have peak GH <3 ng/ml and peak cortisol <550 nmol/ml in GST, ITT is required. Because the sample is small GST can’t substitute ITT now. The study continues.

DO: 10.1530/endoabs.32.P704

P705
Diurnal melatonin profile in patients with acromegaly
Oksana Khyzhnyak, Myroslava Mykytyuk, Tatayna Sulima & Yuri Karachentsev
Institute for Endocrine Pathology Problems, Kharkiv, Ukraine.

Introduction
Cardiovascular complications are the most relevant cause of mortality in patients with acromegaly. Aims
To evaluate the association of diurnal melatonin profile with arterial hypertension in acromegalic patients.

Subjects and methods
Thirty seven patients (15 men and 22 women; aged 18–75 years) with acromegaly were under investigation. Blood samples for GH and IGF1 were taken in fasting state. 6-Sulfatoxymelatonin (6-SMT), the main melatonin metabolite, was determined by fluorometric assay by C. Druex in two separated urine portions: in the daytime (6-SMTd) and nighttime (6-SMTn). Routine measurements of blood pressure (BP) were done. The average of three measurements with a mercury sphygmomanometer was used in all analysis. The BP varied in large SBP (80–176 mm/Hg); DBP (58–116 mm/Hg). Arterial hypertension (AH) was diagnosed when BP was above 140/90 mm/Hg. Disease activity was evaluated according to the Consensus Conference criteria (2000). Data are given as mean±S.E.M. and nonlinear regression model equations parameters.

Results
In patients with somatotropinoma (GH, 22.8 ± 3.5 ng/ml) and somatomamotropinoma (GH, 26.3 ± 5.3 ng/ml) the diurnal level of 6-SMT (96.5 ± 9.8 nmol) including 6-SMTd (46.8 ± 5.6 nmol) and 6-SMTd (49.7 ± 5.6 nmol), 6-SMTd/6-SMTd (1.46 ± 0.22) have been found out. It was revealed that in patient without AH the modulating action of melatonin on DBP is approximated by equations: DBP = 48.2 + 7.2 x ln(6-SMTd) (R² = 37.9%; r = 0.61; P = 0.02).

In patient with AH the negative associations exist between level of 6-SMTd and SBP (R² = 27.8%; r = −0.52; P = 0.01), and 6-SMTd and DBP (R² = 47.8%; r = −0.69; P = 0.004). The 90% of patient with AH have the diurnal level of 6-SMT <120 nmol including 6-SMTd <80 nmol and 6-SMTd <40 nmol.

Conclusion
In patients with active acromegaly AH is associated with 6-SMTd <120 nmol and 6-SMTd/6-SMTh >1. For hypertensive patients with acromegaly decreased level of melatonin in nighttime is more appropriate than in daytime. Altered diurnal profile of melatonin may be one of the cause of AH in patients with acromegaly.

DOI: 10.1530/endoabs.32.P705

P706
Comparative analysis of the hormonal, MRI and morphological characteristics of patients with Cushings disease remission and no remission after neurosurgical treatment
Eugenia Marova, Svetlana Arapova, Galina Kolesnikova, Anastasiya Lapshina & Ludmila Rozhinskaya
National Endocrine Research Center, Moscow, Russia.
Introduction
Long term remission of CD is achieved in 65–83% after neurosurgery, while the remaining cases have recurrence or continued tumor growth. This paper deals with the problem of CD prognostic factors after neurosurgery.

Design
ACTH and cortisol blood levels, free cortisol in daily urine, MRI, histology (hematoxyline–eosine staining) and immunohistochemistry (with antibodies to the pituitary tropic hormones, Ki-67, CD31 and VEGF) of the removed corticotropinomas tissue were compared between two groups of patients with CD (totally 46): 31 (67.4%) patients in remission (first group) and 15 patients (32.6%) without CD remission (second group) after neurosurgery, who were observed on average for 2 years.

Results
ACTH and cortisol blood levels didn’t differ between two groups of patients before neurosurgical treatment ($P = 0.9$ and $P = 0.8$ respectively). The content of free cortisol in the daily urine before treatment was significantly higher in patients from the second group ($P = 0.0006$). Volume and topography of corticotropinomas on MRI also didn’t differ in patients from both groups ($P = 0.8$ and $P = 0.9$ respectively). After pituitary adenomectomy in 30 (69.6%) patients from the first group developed clinical and laboratory signs of adrenal insufficiency, whereas only 5 (10.9%) patients from the second group were diagnosed with adrenal insufficiency. Histologically the incidence of basophilic-cell tumors ($P = 0.4$), naitosis ($P = 0.9$), necrosis ($P = 0.5$), hemorrhage ($P = 0.7$), stromal edema ($P = 0.9$), angiomatosis ($P = 0.6$) and anterior pituitary hyperplasia ($P = 0.5$) didn’t differ in the corticotropinomas of patients from the both groups. Significant difference of frequency of mono- ($P = 0.8$), bi- ($P = 0.8$) and polihormonal ($P = 0.4$) adenomas in patients from the both groups is not found. Labeling index of Ki-67 in corticotropinomas in patients without CD remission was significantly higher than in adenomas of patients with remission ($P = 0.02$). Significant differences of CD31 ($P = 0.3$) and VEGF ($P = 0.7$) expression in the tumors of patients from both groups did not find.

Conclusion
Such factors as the level of free cortisol in the daily urine, the absence of adrenal insufficiency after neurosurgery, increased labeling index of Ki-67 may be considered as poor prognostic factors of CD after neurosurgery.

DOI: 10.1530/endoabs.32.P707

P707
Prevalence and clinical significance of hook-effect and macroprolactinaemia phenomenons in patients with prolactinomas
Farida Nasibullina1, Gulnar Vagapaova1-2 & Bakhtiyar Pashaev1
1 Kazan State medical Academy, Kazan, Russia; 2 Kazan State Medical Institution, Kazan, Russia.

Introduction.
Circulating prolactin is predominantly monomeric, but when there presents more than 60% of polymeric, less bioactive forms, phenomenon of macroprolactinemia is diagnosed. For prolactinomas, serum prolactin levels generally parallel to tumor size, but tumor mass and prolactin levels may be dissociated due to hook-effect, when circulating prolactin is predominantly monomeric, but when there presents more than 60% of polymeric, less bioactive forms, phenomenon of macroprolactinemia in patients with prolactinomas is diagnosed.

Materials and methods
190 patients with prolactinomas (87% females and 13% males) were examined with conventional laboratory and instrumental methods. Pituitary tumors were classified according to size as microadenomas – < 10 mm, mesoadenomas – from 10 to 20 mm, macroadenomas – from 20 to 40 mm, giant – > 40 mm in diameter. Results:
Macroprolactin was revealed in 65 cases (34%) of asymptomatic hyperprolactinemia. Phenomenon of macroprolactinaemia was found in 5% of patients with microadenomas, and was negative in patients with other tumor sizes ($P < 0.01$). Average prolactin content in those patients was 1550 ± 1.7 mU/l. Average macroprolactin content was 64.5 ± 4%. Hook-effect phenomenon was observed in 3 patients with prolactin level of 322 168 mU/l, 318 785 mU/l, from 4200 to 240 168 mU/l after dilution. In patients with other tumor size this phenomenon was negative ($P < 0.01$).

Conclusion
As phenomenons of macroprolactinaemia and hook-effect cannot be reliably distinguished on clinical criteria alone, we recommend routine screening for macroprolactin in patients with asymptomatic microprolactinomas and hook-effect exclusion by serum dilution in patients with macroadenomas in order to avoid misdiagnosis and mismanagement.

DOI: 10.1530/endoabs.32.P708

P708
Hypoponatremia in the emergency room: characteristics, and initial diagnostic approach
Martin Cuesta Hernandez, Emilia Gomez Hoyos, Francisco Fernandez Capel, Teresa Ruiz Gracia, Alfonso Calle Pascual, Javier Martin Sanchez & Isabelle Runkle De La Vega
Hospital Clinico San Carlos, Madrid, Spain.

Introduction
Hypoponatremia is common in the emergency room, albeit frequently overlooked. Our objective was to describe the characteristics of hypoponatremia in a cohort of emergency room patients, and evaluate how hypoponatremia was studied and followed up.

Material and methods
We studied all 211 patients under 70 years-of-age who presented/developed non-translocational hypoponatremia (serum sodium (SNa) < 135 mmol/l) during the first 48 h of their stay at the emergency room of our general hospital in August 2012. Patients are classified by physical examination and the presence of hemodilution or hemoconcentration (urea/creatinine, hematocrit).

Results
Average age was 47 (s.d. 16), 54.5% (115) were women. 31% (66) had presented hypoponatremia previously. 8.5% (18) were hypovolemic, 3.3% (7) hypervolemic, 62.6% (132) euclidean (64.8% of whom experienced pain, 40.8% nausea, 29% both), 25.6% (54) lacked sufficient data for classification. Mean initial SNa: 132.3 mmol/l (s.d. 3.35). Mean nadir SNa: 131.6 mmol/l (s.d. 3). 5.6% (12) presented polydipsia. 31.8% (67) were medicated with selective serotonin reuptake inhibitors, 6.6% (14) thiazides, 6.6% (14) opiates, 7.6% (16) benzodiazepines, 6.6% (14) antiepileptics, 2.8% (6) antipsychotics. Only 7 (3.3%) patients had osmolality (plasma/urine) determined, 13 (6.2%) urine electrolytes. 21% had TSH levels. Only two patients had cortisol level measured. A comprehensive diagnostic study of hypoponatremia (physical exploration and laboratory tests) was undertaken only by Endocrinologists. In 34% (72) SNa levels improved within 24 h, in 17.5% (37) they dropped. In the rest SNa remained stable or was not repeated. 2.8% (6) developed overcorrection of SNa. None were relowered. The most common principal diagnoses were urinary tract infection: 10.5% (22), neoplasia: 8.5% (18) – a third of whom had ENT cancer – and gastroenteritis: 7.6% (16). In 1.4% (3) hypoponatremia was the principal diagnosis and in 15.2% (32) a codified diagnosis. After discharge, 36% (27) of the 75 patients with follow-up data remained hypoponatremic.

Conclusions
In a majority of cases, hypoponatremia was inadequately studied in the emergency room of our hospital, hindering a correct diagnosis and treatment of this important disorder.

DOI: 10.1530/endoabs.32.P709

P709
Modulation of Na+ / K+ -ATPase activity of rat brain synaptosome by norepinephrine and serotonin
Sukra Sinha
University of Allahabad, Allahabad, U.P, India.

Sleep and wakefulness are behavioral and physiological activities. It is a modified form of the basic rest activity cycle. Humans usually fall asleep by entering in non Rapid Eye movement sleep, a phase accompanied by characteristic changes in
the encephalogram (EEG). The person next moves to REM sleep, which is characterized not only by rapid eye movements but also by inhibition of skeletal muscle tone. These two states alternate with each other during sleep cycle. It has been found that REM sleep is generated as a result of excitation of Cholinergic PS on neurons and inhibition of monoaminergic PS off neurons. Moreover the REM sleep deprivation induced increase in Na+/K+ ATPase activity which is partially mediated by NE. Serotonin has been found to increase during REM sleep. These facts implicate that both serotonin and norepinephrine are partially mediated by NE. Serotonin has been found to increase during Na+/K+ ATPase activity. Brain from the male wistar rats weighing 250-280 g was extracted and submitted to homogenization, synaptosomes was prepared and Na+/K+-ATPase activity was estimated under the influence of NE (100 μM), 5HT (μM), prazosin (5 mM) and propranolol(5 mM) in different combinations. Both NE and 5HT increase the Na+/K+ ATPase activity individually and also synergistically when used in combination but in presence of receptor antagonists a decrease is observed. Moreover prazosin and propranolol also decrease the basal values of Na+/K+ ATPase activity. We conclude that results will help in exploring the therapeutic possibilities for neurological and other movement disorders associated with norepinephrine and serotonin.

DOI: 10.1530/endoabs.32.P709

P710
Adulthood germ cell tumor: a case report
Joana Menezes Nunes, Elisabete Rodrigues, Josué Pereira, Raquel Portugal, Lígia Castro, Irene Bernardes, Lígia Osório, Olinda Faria & Davide Carvalho
Centro Hospitalar São João, Porto, Portugal.

Introduction
Germ cell tumors (GCTs) are classified as extragonadal if there is no evidence of a primary tumor in the gonads. They typically occur in the midline structures. Newly diagnosed adult cases of pituitary or pineal glands germinomas are very rare since most of the cases are diagnosed in the mid teens, presenting 1:14.1, on behalf of the male gender. The estimated incidence of this tumor in western countries is between 0.4–3.4%, being more frequent in the Asia.

Case report
A 30-year-old man, was referred to Endocrinology in August 2007, complaining of lack of energy, asthenia, decreased body hair, decreased libido and erectile dysfunction, with no ejaculate, since December 2005. He was previously observed by Urology, carried out thyroid function and was medicated with levothyroxine 100 μg/day since March 2007. Decreased hairiness (axillary, trunk and beard) and decreased testicular volume, without other major changes on physical exam. In October 2007, starts complaints of headaches and blurred left vision. The patient was observed by Ophthalmology, which diagnosed bitemporal hemianopsia, and performed pituitary MRI which revealed a bulky suprasellar lesion with 16×23×20 mm. The endocrinological evaluation revealed hypo- tuitarism. He underwent pituitary surgery at May 2008, with near total resection, because of proximity to the optic chiasm. The histological exam revealed germ cell tumor. According to the radiosensitive of these tumors treatment was completed with external radiotherapy. After surgery, the hormonal evaluation showed panhypopituitarism and diabetes insipidus. The patient remains clinically stable, on hormonal replacement therapy and without evidence of recurrence.

Discussion
Owing to its rarity in adulthood, not only by location but also to its multifaceted clinical presentation, requires multidisciplinary assessment. The cranial location requires surgical treatment which is often near total resection, because of risk of surgical complications. Therefore, radiation therapy is usually necessary. Intracranial germinomas have a reported 90% five years survival, so follow-up should be extensive.

DOI: 10.1530/endoabs.32.P710

P711
Infraesellar gangliocytoma causing cushing’s disease: a case report
Marie-Eve Domingue1, Christian Raftopoulos2 & Dominique Maiter1
1Cliniques Universitaires Saint Luc UCL, Bruxelles, Belgium; 2Clinique Saint-Pierre, Ottignies, Belgium

Gangliocytomas are uncommon neuronal tumors that can sometimes cause endocrine syndromes. A few such cases have been reported in association with Cushing’s disease. In most cases, the tumor contained CRH and was associated with pituitary corticotroph hyperplasia or adenoma (mixed lesion). Only one case of isolated gangliocytoma causing Cushing’s disease per se has been described.

We report the case of a 62-year-old woman whose clinical picture and endocrine testing clearly demonstrated ACTH-dependent Cushing’s syndrome. Pituitary MRI showed a 12 mm homogeneous, T2-weighted hyperintense, infrasellar mass with delayed contrast enhancement. The mass was bulging into the sphenoidal sinus with scalloping of the clivus. Transphenoidal surgery was performed and allowed complete resection of the tumor with sparing of the whole normal anterior pituitary. Very low postoperative serum cortisol and ACTH levels were observed, both in the early postoperative period and one month later, proving that the resected lesion was entirely responsible for the clinical picture. Pathology and immunohistochemistry demonstrated a benign tumor composed of mature neuronal cells most likely arising from the posterior pituitary, resembling hypothalamic ganglion cells and expressing ACTH. The gangliocytoma was surrounded by a rim of pituitary tissue containing some ACTH-producing endocrine cells. Careful analysis of the resected lesion did not reveal any pituitary microadenoma. CRH immunostaining of the tissue is currently being performed in order to determine whether the gangliocytoma was also responsible for an associated CRH-induced corticotroph hyperplasia.

This infrasellar ACTH-containing gangliocytoma singles out the few reported cases in which gangliocytomas cause endocrine abnormalities via hypothalamic hyperplasia or adenoma. Further analyses on the resected tissue will hopefully allow us to better describe the case of our patient and contribute to the understanding of this rare entity.

DOI: 10.1530/endoabs.32.P711

P712
Effects of GH therapy in carbohydrate metabolism in spanish adults with GH deficiency
Paola Andrea Parra Ramírez, Laura Pérez Fernández, Alberto Fernández Martínez, Cristina Grande Aragón & Cristina Alvarez-Escolá
La Paz University Hospital, Madrid, Spain.

GH deficiency (GHD) in adults is characterized by a tendency towards fat mass gain and may predispose to type 2 diabetes mellitus. GH replacement (GHR) is associated with impaired insulin sensitivity shortly after starting therapy, reflected by increased fasting glucose and insulin levels. Available evidence suggests that correlates regarding glucose intolerance in patients receiving long-term GHR have not been substantiated. However, several environmental and lifestyle-related factors could influence glucose abnormalities in patients with GHD, and no study has specifically addressed this issue in Spanish patients. Thus, we aimed to describe the evolution of carbohydrate metabolism (fasting glucose (FG) and HbA1c) and ascertain possible risk factors for developing glucose abnormalities in adult patients receiving GHR.

We analyzed retrospectively 34 GHD adults (mean age 40.4 years; 16 females) from our centre who received GHR for at least 2 years (mean duration of treatment was 7.4 years). FG, HbA1c and anthropometric parameters were measured before starting treatment and at the end of the follow-up. Associations were tested by Mann–Whitney U test between baseline variables (age, BMI, total body fat, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, mean maintenance dose of GH, and glucocorticoid replacement) and these metabolic variables.

None were diabetic at baseline. FG and HbA1c were significantly higher at the end of follow-up when compared to baseline (+6.7 (S.O.11.08) mg/dl P=0.001 and +0.2 (S.O.0.4) % P=0.014 respectively). Average HbA1c increase was 0.23%. No significant changes were observed in BMI or body composition. Six patients had dysglycemia, 4 (11.7%) developed diabetes and 2 (5.7%) impaired fasting glucose. However, no predefined baseline traits were significantly related to the metabolic derangements, including glucocorticoid replacement.

In conclusion, our results indicate that long-term GHR mildly increases FG and HbA1c. Current hydrocortisone replacement regime was not associated with dysglycemia in our series.

DOI: 10.1530/endoabs.32.P712
P713
Clinical case of silent corticotropinoma
Larisa Dzeranova, Anna Lipatenkova, Ekaterina Pigarova & Iya Voronkova
Federal State Research Centre for Endocrinology, Moscow, Russia.

Silent corticotropinomas (SCAs) are a subtype of non-functioning pituitary adenomas (NFPA) demonstrating positive immunoreactivity for ACTH, but without clinical or biochemical features of hypercortisolism. SCAs typically present as macroadenomas with symptoms related to a local mass effect. In some cases SCAs can transform into hormonal active formations with gradually developing symptoms of hypercortisolism.

The aim
To describe a patient with NFPA who over time developed a biochemical only presence of hypercortisolism.

A case description
A young woman presented at the age of 25 years with headaches and oligomenorrhea. The hormonal tests showed the moderate hyperprolactinemia 28.5 ng/ml (n <19.5) with the absence of macroprolactin, normal levels of TSH, IGFI, ACTH, cortisol, LH, FSH, the MRI revealed pituitary macroadenoma 1.5×1.2 cm with the trend toward suprasellar extension. Short-term medical treatment with low doses of dopamine agonists resulted in drop of prolactin levels below reference values and normalization of menstrual function, which was consistent with the diagnosis of NFPA with hyperprolactinemia due to local mass effect. At the next follow-up 2 years later the patient complained of headaches, weakness and psycho-emotional instability. Lab data revealed high levels of ACTH/cortisol, absence of cortisol suppression at the 1 mg dexamethasone test, and a significant suppression at 8 mg dexamethasone test. The MRI-scan didn’t detect any growth of the adenoma. Remarkably, the patient did not have any clinical features of hypercortisolism (BMI 20.5 kg/m², fat distribution, absence of striae and hyperpigmentation, normal levels of blood pressure and blood sugar levels, osteopenia, but no osteoporosis or fractures). At age of 28 years the patient underwent a transnasal adenomectomy with developing of pain syndrome. Levothyroxine and testosterone therapy were commenced due to progressive failure of the gonadal and the thyroid axis. Nowadays, he has begun chemotherapy and corticotherapy.

Results
A mutation in the codon 634 of the RET gene (c.1899G>T) was detected by DNA sequencing and/or restriction enzyme analysis. The patient died in 2013 when he was 32 years old.

Conclusion
Our case is consistent with SCA, with limited clinical features of corticosteroid excess.

P714
Central diabetes insipidus, as the first sign of Langerhans cell histiocytosis in an adult
Nereza Egața1, Irune Ruiz2, Ismene Bilbao1, Maite Aramburu1, Alfredo Yoldi1, Cristina García1, Mariano Alvarez Coca1, Maria Luisa Antuñano1 & Miguel Goena1
Endocrinology, Hospital Domostia, San Sebastian, Spain, 2Pathology, Hospital Domostia, San Sebastian, Spain.

Introduction
Langerhans cell histiocytosis (LCH) may be localized or be a systemic disease. The diagnosis is frequent in pediatric age. In adults, infiltration is most frequently in bones, lungs and skin, and shows particular predilection for hypothalamo-pituitary axis.

Case
A 51 years old man was referred due to polyuria of ~ 15 l of daily urine output. His past medical history revealed bronchiectasis and skin problems. Laboratory test demonstrated hypernatremia, decreased urinary and increased serum osmolalities. Water deprivation test was not held due to severe signs of dehydration. Pituitary MRI showed enhancing pituitary signal with thickened stalk and loss of the bright spot of the neurohypophysis. Desmopressin was started with a presumptive diagnosis of insipidus diabetes and urine output and biochemical tests returned to normal. Anterior pituitary hormones were normal. Months later, he presents temporal cephalea and MRI revealed two subcortical lesions. Neurosurgery was practiced and histology confirmed Langerhans cell proliferation. His skin and lungs were also affected. Levotheroxine and testosterone therapy were commenced due to progressive failure of the gonadal and the thyroid axis. Nowadays, he has begun chemotheraphy and corticotherapy.

Conclusion
i) Although LCH is mainly considered a pediatric disease, it may be diagnosed in adults; ii) the difficulty in making an accurate diagnosis is reflected in the long time that takes from the onset of the symptoms to the diagnosis, due to the fact that patients visit many different specialists, the lack of clinical suspicion, and the variable characteristics of the disease; and iii) LCH is a multisystemic disease and multidisciplinary management is important.

P715
RET codon 618 mutation is the most frequent genotype in saudi families with multiple endocrine neoplasia type 2a and familial medullary thyroid carcinoma
Faiza Qari & Tariq Nasser
King Abdulaziz, Jeddah, Saudi Arabia.

Background and objectives
Certain diseases, such as multiple endocrine neoplasia type 2A (MEN2A), MEN2B, familial and sporadic medullary thyroid carcinoma (MTC) and renal dysgenesis are related to abnormalities of the RET protein. Our aim was to evaluate the frequency of RET mutation in ten Saudi families with MEN2A and familial medullary thyroid carcinoma.

Design and setting
Cross-sectional prospective study of patients followed up at King Abdul-Aziz University Hospital and King Abdul-Aziz Medical City, Jeddah between March 2001 and March 2011.

Patients and methods
Genomic DNA was isolated from peripheral blood leucocytes of all the subjects using standard procedures. Exons 10, 11, 13, 14 and 16 of the RET proto-oncogene were analyzed by single-strand conformation polymorphism, direct DNA sequencing and/or restriction enzyme analysis. Statistical analysis was performed using the Statistical Package for the Social Sciences.

Results
Seventy-nine subjects were screened for RET mutation. Forty-three of the subjects with hereditary MTC were enrolled in this study. MEN2A was identified in 25 cases; MTC was diagnosed in all 25 cases (100%), pheochromocytoma in 13 cases (52%) and hyperparathyroidism in 4 cases (16%). The most frequent genotype in patients with MEN2A syndrome was codon 618 mutation (46.6%), followed by codon 634 mutation (44.2%). Among the five families with MEN2A, three had a mutation at codon 634, while two had a mutation at codon 618.

Conclusion
The most frequent RET proto-oncogene mutation in our series was codon 618 (exon 10).

P716
Neurological manifestations of Vitamin D deficiency, is there any significant clinical correlation?
Faiza Qari & Tariq Nasser
King Abdulaziz, Jeddah, Saudi Arabia.  

Objective
The objective of this study was to investigate the correlation between the neurological manifestations of Vitamin D deficiency and the levels of 25(OH)D and bone profile.

Methods
We conducted a case series study in patients with osteomalacia who were followed up at King Abdulaziz Medical City, Jeddah, between January 2010 and December 2011. We collected information on demographic data, etiological factors for Vitamin D deficiency, clinical presentations (typical and neurological), and radiological findings. T test was used to determine whether there was a correlation between the neurological manifestations of Vitamin D deficiency and vitamin D levels and bone profile. A P-value <0.05 was considered significant.

Results
Sixty patients were enrolled in the study. Atypical presentations included progressive muscle weakness (proximal more than distal) in 73% of the cases and gait disturbances in 61.7% of the patients. There was no significant correlation between neurological manifestations and the bone profile or vitamin D levels. Significant correlations existed only between the inability to walk and the levels of serum calcium and phosphate, with P-values of 0.043 and 0.037, respectively.
P717

Craniopharyngioma – a diagnosis not to be missed

Joana Menezes Nunes, Elisabete Rodrigues, Sérgio Salvador, António Cerejo, Ricardo Reis, Sérgio Silva, Luís Augusto, Marcos Guimarães, Rui Vaz & Davide Carvalho
Centro Hospitalar São João, Porto, Portugal.

Introduction

Craniopharyngiomas are intracranial tumors that develop from Rathke’s pouch rests of epithelium. They have a bimodal age distribution, with peak incidence at childhood and in the adult/elderly, although in our series we have more patients in a middle peak. Usually they are benign but responsible for significant morbidity, particularly when located near critical structures such as optic chiasm, pituitary gland and hypotalamus, and thus might cause visual, neurological and endocrine deficits.

Case report

A 24-year-old male, asymptomatic until January/2011, when started complaining of progressive visual impairment of the left eye (5/10), relative afferent pupillary defect, and pallor of optic disc in the inferior right location. Clinically the patient maintains visual impairment of the right eye (<1/10), relative afferent pupillary defect, and pallor of optic disc in ophthalmoscopy, without other neurological or endocrine symptoms.

Conclusion

Craniopharyngiomas are rare tumors, often with suprasellar extension. Early diagnosis and treatment require a high diagnostic accuracy when dealing with visual impairment, neurological and hormonal symptoms. They tend to invade locally and relapse after treatment, requiring a long follow-up.

DO: 10.1530/endoabs.32.P717

P718

Features of family inheritance in patients of non-functional pituitary adenomas in Uzbekistan

Zamira Khalimova1,2, Dilorom Sharipova1,2, Rozshan Fayzullaev1,2, Yulduz Urmanova1,2, Dinara Alieva1,2, Gulrukhi Alimakhamedova1,2, Munira Karimova1,2 & Shokhsanam Safarova1,2

1Instituto de Investigaciones Biomedicas Alberto Sols CSIC-UAM, Madrid, Spain; 2Department of Anatomy, Histology and Neuroscience, School of Medicine, UAM, Madrid, Spain.

Abstract withdrawn.

DO: 10.1530/endoabs.32.P718.1

P719

The nuclear corepressor NCoR is an essential mediator of the anti-tumorigenic and anti-metastatic actions of the thyroid hormone receptor

Olaia Martínez-Igesias1, Rosa M Martin-Orozco1, Elvira Alonso Merino1, Juan Pedro Velasco-Martín2, Javier Regadera2 & Ana Aranda1

1Instituto de Investigaciones Biomédicas Alberto Sols CSIC-UAM, Madrid, Madrid, Spain; 2Department of Anatomy, Histology and Neuroscience, School of Medicine, UAM, Madrid, Spain.

Reduced expression or activity of the thyroid hormone receptors (TRs) are common events in cancer, suggesting that these receptors could act as tumor suppressors. We have previously shown that TRβ expression in SK-hep1 hepatocarcinoma cells (SK-TRβ cells), reduces tumor growth and strikingly inhibits invasion, extravasation, and metastasis formation in nude mice. These effects could be related to a decreased expression in these cells of prometastatic genes, such as COX2, MMP9 or ID1. We have now found that transcripts for these genes are also decreased in tumors and metastasis originated by SK-TRβ cells in nude mice. Using transient transfection assays, we have localized CRE, AP1 and SPI sites in their promoters that appear to mediate the inhibitory effect of TRβ. This suggests that cross-talk with other transcription factors plays an important role in the repression of prometastatic gene transcription by the receptor. One mechanism that could explain suppression of prometastatic gene expression by TRβ is the recruitment of co-repressor complexes. Indeed, we found that expression of the corepressor NcoR is significantly higher in SK-TRβ cells than in parental cells and is also increased in tumors and metastasis. NcoR silencing with interference RNA produces a strong increase in transcript levels of several prometastatic genes and enhances cellular invasion in matrigel assays. These effects appear to be specific for NcoR, since depletion of the corepressor SMRT is ineffective. Furthermore, NCoR silencing reverses significantly the effect of TRβ expression, enhancing tumor growth and invasion, extravasation and metastasis development when cells are inoculated into nude mice. These changes are associated with increased expression of prometastatic genes in the tumors and in the metastatic injuries. These results demonstrate the essential role of the co-repressor NcoR in the tumor suppressive actions of TRβ, and suggest the importance of the corepressor as a potential therapeutic target in cancer.

DO: 10.1530/endoabs.32.P719

Endocrine Abstracts (2013) Vol 32
The sex hormone 17β-estradiol (E2) exerts its pleiotropic effects through the binding to the ligand-activated transcription factor estrogen receptor alpha (ERα). The ERα complex regulates several physiological processes including cell survival and proliferation through transcriptional (i.e., estrogen responsive element (ERE)-based gene transcription) and non-transcriptional membrane-initiated effects (i.e., activation of signalling cascades). Many post-translational modifications occur on ERα and are regulated by E2. Indeed, E2 induces ERα phosphorylation that facilitates ERα-dependent gene transcription while the hormone reduces ERα palmitoylation, thus modulating the amount of the receptor located at the plasma membrane and the E2 signalling to cell proliferation. The ERα is also an ubiquitinated protein: ERα polyubiquitination (polyUb) increases upon E2 binding and E2-dependent ERα degradation occurs in parallel to the appearance of the E2-evoked physiological effects. However, the role of ERα post-translational modifications in the regulation of the E2-dependent cell proliferation is poorly appreciated. Therefore, we analyzed here how ERα phosphorylation, palmitoylation and ubiquitination influence E2-induced cell proliferation in an integrated manner.

Our results demonstrate that the polyUb-based ERα degradation cross-talks with receptor phosphorylation and palmitoylation and is required for the E2-dependent control of cell proliferation. Furthermore, the lack of ERα palmitoylation fosters E2-induced polyUb-dependent ERα degradation and prevents both receptor phosphorylation and E2-dependent cell proliferation. Therefore, these data demonstrate that a code of diverse post-translational modifications occurs on ERα and uncover a new model of E2: ERα cellular signalling in which the E2-dependent control of ERα post-translational modifications finely coordinates the E2 ability to regulate cell proliferation.

DOI: 10.1530/endoabs.32.P720

P721
Non-proteolytic ubiquitin-based signalling regulates estrogen receptor α activities
Valeria Pesiri & Filippo Acconcia
Section Biomedical Science and Technologies, TREP Department of Science, University Roma, Rome, Italy.

Protein ubiquitination modulates many physiological processes (e.g. cell proliferation). The ubiquitin-based signalling consists in both proteolytic and non-proteolytic functions: the first ones require modification of the target protein with polyubiquitination, a modification that induces the activation of the 26S-proteasome, whereas the second ones can be based on protein monoubiquitination. The recognition of ubiquitination diversity is dependent on specific Ub receptors that bind to the ubiquitinated protein by contacting the Ub-modification systems. The recognition of ubiquitination diversity is dependent on specific Ub receptors that bind to the ubiquitinated protein by contacting the Ub-modification systems. The recognition of ubiquitination diversity is dependent on specific Ub receptors that bind to the ubiquitinated protein by contacting the Ub-modification systems. Estrogen receptor α (ERα) is a ligand-activated nuclear receptor that mediates the cellular effects of the steroid hormone 17β-estradiol (E2). ERα-based signalling is a function of receptor intracellular localization. While ERα nuclear localization is required for E2-induced gene transcription, the ERα extra-nuclear localization is necessary to trigger the rapid activation of several signalling kinase cascades (e.g. ERK/MAPK, PI3K/AKT). Recent data provided the initial evidence that proteolytic and non-proteolytic Ub-based functions modulate ERα activities. ERα is a monoubiquitinated protein but the monoubiquitination-dependent regulation of the ERα activities that lead to the activation of cell proliferation are not known. Furthermore, the fact that ERα is a monoubiquitinated protein opens the possibility that an Ub could be present within the ERα structure and that the receptor could behave as an ubiquitin receptor. However, whether non-covalent Ub: ERα binding could occur and play a role in E2: ERα signalling is unknown. Here, we show that mutation of the ERα monoubiquitination sites prevents the E2: ERα-mediated activation of signalling pathways to cell proliferation, in addition, a previously unrecognized Ub-binding surface has been found within the ERα and contribute to the E2 transcriptional activity. Altogether, these data indicate that the ERα belongs to the Ub-based signalling network and that receptor monoubiquitination as well as non-covalent Ub binding regulate ERα functions in a non-proteolytic manner.

DOI: 10.1530/endoabs.32.P721

P722
The thyroid hormone receptors inhibit invasive and fibrotic responses to TGFβ by transcriptional cross-talk with smad-transcription factors
Elvira Alonso-Merino1, Rosa M Martín-Orozco2, Lidia Ruiz-Llorente1, Luisa Fernandez Fanjul-Rodriguez1, Oliva Martínez-Iglesias1, Juan Pedro Velasco-Martín2, Javier Regadera2 & Ana Aranda1
1Instituto De Investigaciones Biomédicas Alberto Sols Csic-Uam, Madrid, Spain; 2Department of Anatomy, Histology and Neuroscience, School of Medicine, Uam, Madrid, Spain.

Transforming growth factor β (TGFβ) signals through activation of Smad transcription factors, which bind to Smad binding elements (SBEs) in target genes. TGFβ can promote cancer cell proliferation and invasion, and plays a key role in the pathogenesis of scleroderma and other fibrotic disorders. We have previously shown that the thyroid hormone receptors (TRs) can block tumor growth and invasion. We now have analyzed the possibility that TRs could antagonize TGFβ-dependent responses. We found that liganded TRs block transcriptional of SBE-containing reporter plasmids by TGFβ, and repress transcription of endogenous TGFβ target genes. The thyroid hormone TRβ reduces Smad phosphorylation by TGFβ and causes a limited inhibition of Smads translation to the nucleus. There is a direct and constitutive protein-protein interaction between TR and Smad transcription factors that could be involved in the observed effects. In chromatin immunoprecipitation assays (ChIP) with SBE-containing promoters, TRβ inhibits TGFβ-dependent recruitment of Smads, reduces acetylated histones and induces recruitment of histone deacetylase 3 (HDAC3). The hormone is also able to block TGFβ-dependent proliferation and migration of cultured cancer cells. The potential anti-fibrotic effect of the TRs was investigated in mice using a model of skin fibrosis induced by subcutaneous injections of bleomycin. In euthyroid mice bleomycin caused a significant increase in dermal thickness, hair loss and high packaging of collagen fibers, characteristic of areas of dermal scleroderma and fibrosis. Topical application of TRβ significantly attenuated fibrosis, with a decrease of dermis thickness, reduced compaction of bundle collagen fibers and more extracellular matrix, associated to a low collagenization of subcutaneous cellular tissue. These results demonstrate that TRβ blocks transcriptional responses to TGFβ, and suggest that some of the actions of the thyroid hormone receptors, both in vivo and in cultured cells, can involve repression of the activity of the TGFβ signalling pathway.

DOI: 10.1530/endoabs.32.P722

P723
5/6 Nephrectomy reduces muscle mitochondria in mice as to decrease exercise endurance associated with further exacerbation by dietary protein
Masanori Tamaki, Kazutoshi Miyashita, Shu Wakino, Masanori Mitsuishi, Koichi Hayashi & Hiroshi Itoh
Department of Internal Medicine, School of Medicine, Keio University, Tokyo, Japan.

Introduction
Chronic kidney disease impairs physical performance from an early stage of disease, and the impairment is a critical medical problem because lowered physical activity correlates with renal prognosis and mortality, and constitutes an independent cardiovascular risk for chronic kidney disease patients, with as high an impact as hypertension and diabetes. In this study, the time course and mechanism of muscle insufficiency in renal failure were investigated using 5/6 nephrectomized (5/6Nx) mice, a model of mild chronic kidney disease. Furthermore, the effect of high-protein diet on chronic kidney disease was examined.

Methods
C57Bl/6 mice which had undergone 5/6 nephrectomy at 6-7 weeks were examined for physical performance in young (16-20 weeks old) and aged (48-52 weeks old) groups. Protein adjusted diets were fed from 8 weeks old. Results
A decrease in muscle mitochondria and running distance was identified in young 5/6Nx mice, despite the preservation of muscle volume and power. Thereafter, a decrease in muscle volume associated with a reduction in muscle power became apparent in aged 5/6Nx mice. Appetite, measured from feeding from 8 weeks old increased muscle volume and power in the mice; however, it further decreased running distance, associated with a decrease in the activity of pyruvate dehydrogenase which promotes aerobic glycolysis. Activation of pyruvate dehydrogenase by dichloacetate effectively recovered running distance which was decreased by dietary protein.

Conclusion
A decrease in muscle mitochondria was identified as a new mechanism for the reduction in exercise endurance of 5/6 nephrectomy mice. Decreased pyruvate
dehydrogenase activity accounted for the further reduction in exercise endurance by dietary protein. These findings clarify the mechanism of muscle insufficiency in renal failure and suggest activation of muscle mitochondria as a potential strategy for the improvement of physical performance of patients with chronic kidney disease.

DOI: 10.1530/endoabs.32.P723

P724
Effects of Tribulus terrestris on immune function in over-trained rats and its mechanism: the role of glucocorticoid and glucocorticoid receptor
Xiaohui Wang, Ru Wang, Liang Yin & Gui Liu
Shanghai University of Sport, Shanghai, China.

Purpose
To investigate the effects of Tribulus terrestris (TT) on immune function in over-trained rats and explore the mechanisms – the role of glucocorticoid (GC) and glucocorticoid receptor (GR).

Methods
Thirty male SD rats were randomly divided into control group, over-trained group and over-trained + TT group. The last two groups were trained on a motor-driven treadmill with a progressively increased load for 6 weeks. The over-trained + TT rats took the medicine by gastric irrigation while the others ingested the same amount of saline. The levels of plasma testosterone and corticosterone were measured by ELISA. The numbers of CD3+ T cells and natural killer (NK) cells were found in the over-trained rats compared with that of non-exercise rats, indicating successful establishment of exercise-related immunosuppression; supplement of TT lead to significant increases of T:C ratio, CD4+ :CD8+ ratio and the amounts of CD4+ cells, NK cells, NKT cells in the over-trained rats; down-regulation of IFNγ and IL4 were detected by flow cytometry.

Results
Distinct decreases of body weight, testosterone:corticosterone (T:C) ratio, numbers of CD3+ T cells and natural killing (NK) cells were found in the over-trained rats compared with that of non-exercise rats, indicating successful establishment of exercise-related immunosuppression; supplement of TT lead to significant increases of T:C ratio, CD4+ :CD8+ ratio and the amounts of CD4+ cells, NK cells, NKT cells in the over-trained rats; down-regulation of IFNγ and IL4 were detected by flow cytometry.

Conclusion
These results indicated that: supplement of TT improved the suppressed immune function resulted from over-training in rats, including increases of CD4+ :CD8+ ratio and the amounts of NK, NKT cells and retrieval of Th1/Th2 balance; the improved effect of TT on suppressed immune function in over-trained rats might be related to the increase of GR and decrease of GC.

DOI: 10.1530/endoabs.32.P724

P725
Nuclear receptor ‘master’ coactivators of physiology and pathology
Bert O’Malley
Baylor College of Medicine, Houston, Texas, USA.

Nuclear receptors control gene expression by recruiting transcriptional coactivators (or corepressors). The coactivators are ‘master regulators’ that coordinate activate multiple distinct transcription factors and target genes and pathways to control major physiologic processes such as reproduction, inflammation, metabolism and growth. Because of their central role as ‘nodes’ of regulation, coactivators are major targets in the development of numerous inherited and acquired endocrine-related pathologies such as infertility, endometriosis, disorders of carbohydrate, lipid and protein metabolism, and numerous cancers. Metabolism and growth are especially prominent pathways for coordinate regulation by coactivators such as SRC-2 and SRC-3. The pleiotropic functions of coactivators in pathways are the result of combinatorial posttranslational modifications of the proteins via enzyme cascades, in conjunction with certain biological isoforms of the proteins. In metabolic diseases and cancers, the intracellular concentrations and the PTM-directed ‘activities’ of the coactivator proteins are critical for ‘driving’ the transcription-dependent physiological outcomes. However, in the case of the cancer cell’s motility or in endometriosis, it is the coactivator protein’s isoforms that are the major mediators of the disease progression. Thus, as a class, the coactivator proteins provide important insights to polygenic diseases. They also may represent new ‘first-in-class’ types of potential targets for therapeutic intervention.

DOI: 10.1530/endoabs.32.P725

P726
Obesity
The lack of Nur77 affects energy and glucose metabolism in females fed on high fat diet
Sonia Pérez Sieira1,2, Gloria Martínez1, Begoña Porteiró1,2, Miguel López1,2, Anxo Vidal1, Rubén Nogueiras1,2 & Carlos Diéguez1,2
1Department of Physiology, School of Medicine–CIMUS, Instituto de Investigaciones Sanitarias (IDIS), Santiago de Compostela, Spain; 2CIBER Fisiopatologia de la Obesidad y Nutricion (CIBERobn), Santiago de Compostela, Spain.

Nur77 is an orphan nuclear receptor included in the NR4A family. This protein has been studied as a transcriptional regulator of glucose metabolism in different tissues. We aimed to investigate the endogenous role of Nur77 on energy and metabolic homeostasis. For this purpose, we used male and female Nur77−/− deficient mice and their wild-type littermates. We challenged them to standard diet and high fat diet, and analyzed different parameters involved in energy balance (food intake, energy expenditure, locomotor activity and respiratory quotient) and glucose metabolism (glucose and insulin tolerance tests).

We found that the lack of Nur77 causes a dimorphic response in the metabolic phenotype of mice fed with high fat diet, being the females more sensitive to high fat diet, while male mice lacking Nur77 were similar to their controls. Female Nur77−/− deficient mice gained more fat mass, an effect that may be explained by the lower energy expenditure in comparison to female wild types. Consistent with the higher amount of fat mass, female Nur77−/− deficient mice showed a lower insulin sensitivity, with no changes in glucose tolerance.

In conclusion, our findings indicate that Nur77 is a potentially important physiological mediator of body weight and insulin sensitivity, particularly in female mice.

DOI: 10.1530/endoabs.32.P726

P727
Abstract unavailable.

DOI: 10.1530/endoabs.32.P727

P728
Serum- and glucocorticoid-regulated kinase 1 in obesity-related adipose tissue and peripheral inflammation
Marie Helene Reiter, Florian Kiefer, Maximilian Zeyda, Chantal Kopecky, Thomas Stulnig, Anton Luger & Greisa Vila
Medical University of Vienna, Vienna, Austria.

The serum- and glucocorticoid-regulated kinase 1 (Sgk1) is a direct transcriptional target of glucocorticoids and is post-translationally activated by the insulin/IGF1 pathway. Distinct polymorphisms in the Sgk1 gene are
associated with increased body weight and type 2 diabetes. Here we investigate the expression and regulation of Sgk1 in human obesity. In both omental and subcutaneous human adipose tissue, Sgk1 expression is significantly increased in 20 obese patients compared to 20 age- and gender-matched controls. Sgk1 protein expression is mainly localised to adipose tissue macrophages. The expression of Sgk1 mRNA in subcutaneous adipose tissue correlates with waist circumference, weight, fat mass and HOMA insulin resistance index, as well as with circulating levels of C-reactive protein (CRP), leptin, interleukin 6 (IL6) and macrophage inflammatory protein 1α (MIP1α). Multiple regression analysis shows that waist circumference, weight, CRP and MIP1α independently predict Sgk1 expression in adipose tissue. In peripheral blood mononuclear cells of eight obese patients compared to eight age- and gender-matched controls, Sgk1 expression is significantly higher in obese subjects. Monocyte-to-macrophage differentiation by phorbol 12-myristate 13-acetate (PMA) strongly induces Sgk1 mRNA expression in the THP1 monocyctic cell line, parallel to increasing IL6 transcription. Lipopolysaccharide (LPS) significantly up-regulates Sgk1 mRNA expression in THP1 monocytes, but has no additional effect on PMA-stimulated Sgk1 in THP1 cells. Taken together, we show increased Sgk1 expression in adipose tissue macrophages as well as circulating mononuclear cells of obese subjects compared to non-obese controls, presenting the first association between Sgk1 and obesity-related inflammation. In addition, our data identify PMA and LPS as novel regulators of Sgk1 in monocyctic cells and suggest a role of Sgk1 in monocyte-to-macrophage differentiation. Further investigation of Sgk1 function in this context might be of therapeutical relevance in obesity-related inflammation and its comorbidities.

DOI: 10.1530/endoabs.32.P728

P729 New insights on molecular mechanisms regulating hepatic sex hormone-binding globulin production: clinical implications in obesity and type 2 diabetes
Cristina Saez-Lopez, Cristina Hernandez, Rafael Simo & David M Selva Research Institute Hospital Vall d’Hebron, Barcelona, Spain.

Human sex hormone-binding globulin (SHBG) is produced and secreted by the liver and it binds androgens and estrogens with high affinity. In blood, SHBG acts as a carrier of these sex steroids and regulates their bioavailability. Low plasma SHBG levels are associated with obesity, abdominal adiposity and metabolic syndrome, and predict the development of type 2 diabetes. In addition, an inverse relationship between plasma SHBG levels and risk of cardiovascular disease has been reported. The SHBG gene has changed its tissue expression and therefore its function during the evolution. Rodents express the SHBG gene in the Sertoli cells of the testis. While in humans, the SHBG gene is expressed in the liver and in the germ cells of the testis. This change of function and tissue expression can be explained by the appearance during evolution of new footprinted regions in the human promoter and an alternative promoter. The generation of human SHBG transgenic mice has allowed us to study the SHBG expression and regulation in vivo. We have used these mice and HepG2 cells to provide evidence that SHBG expression is downregulated by monosaccharides describing the underlying molecular mechanism. We have also demonstrated that proinflammatory cytokines (TNFα and IL1β) downregulates SHBG production by reducing HNF4α levels. These findings give a new explanation by which those patients suffering from chronic inflammation diseases such as obesity and type 2 diabetes have also low levels of SHBG. Noteworthy, our in vitro and in vivo studies showed that insulin does not regulate hepatic SHBG production. This finding contravenes the classic assumption that insulin is the primary regulator of SHBG production in the liver. Finally, we have generated a new mouse model by crossing the human SHBG transgenic mice with the db/db mice. The generation of these mice has allowed us to study the regulation of the human SHBG during the development of obesity. As occurs in human obese subjects, these mice showed low plasma SHBG levels as well as low total and free testosterone levels. This model will permit us to further explore SHBG regulation and to design new therapeutical approaches.

DOI: 10.1530/endoabs.32.P729

P730 Obesity: a paradox in the mortality of the elderly
Haleh Ghaem Maralani1, Bee Choo Tai1, Tian Yin Wong1, E Shyong Tai1, Jialiang Li2, Jie Jin Wang3 & Paul Mitchell3
1University of Singapore, Singapore, Singapore; 2University of Sydney, Sydney, Australia.

Introduction
The effect of BMI on mortality amongst the elderly may be different from younger adults. Thus, this study aims to determine the relationship between BMI and its 5-year changes on all-cause and cause-specific mortality in the elderly. Methods During 1992–1994, the Blue Mountains Eye Study recruited 3654 residents aged ≥49 years in Sydney, Australia. Of these, 75% of survivors returned for follow-up at 5 years. We initially examined the relationship between baseline BMI and mortality nonparametrically using cubic spline. Cox and competing risk models were used to assess associations of baseline BMI and its 5-year changes with all-cause and cause-specific mortality. Results Underweight persons were more likely to be older (mean 66.9, s.d. 9.9 years) and predominantly female (74%). Conversely, obese persons were more likely to be younger (mean 63.7, s.d. 8.3 years), and to have a history of pre-existing disease (hypertension, diabetes, angina, AMI and stroke; 54.5%). Amongst subjects without pre-existing disease, the relationship between baseline BMI and all-cause mortality was U-shaped, with the underweight and obese groups being predisposed to have a greater risk of death. In particular, obesity was associated with coronary heart disease (CHD; hazard ratio (HR) 2.78, 95% CI: 1.34–5.77) and cancer (HR 1.90, 95% CI: 1.08–3.12) deaths. For subjects with pre-existing disease, however, an inverse relationship was observed, with the underweight having a lower risk of death. Five-year reductions in BMI were associated with all-cause, cancer and CHD deaths. Conclusion Obesity affects all-cause, CHD and cancer mortality only amongst the elderly without pre-existing disease. BMI loss was associated with major causes of mortality. Understanding the varying impact of obesity on mortality amongst the elderly with and without pre-existing disease will provide clinicians and public health policymakers with critical evidence for disease management, resource planning and allocation.

DOI: 10.1530/endoabs.32.P730
Bucharest, Romania.

Psychiatry Department, Carol Davila University of Medicine and Pharmacy,

adipose depots (eWAT), undergoing standard diet (SD) or high-fat diet (HFD) from the 8th to 20th

epididymal (eWAT) adipose tissues, obtained from CB1KO (CBN) and

studies on bigger populations are necessary. Nevertheless this results show the

The small number of patients is for clear a limitation, therefore we find that

Conclusions

concentration and cholesterole levels.

than 5kg and there could be observed slight elevations in plasma trigliceride

parameters but at the 6 months measurement 58% of the patients had gained more

Results

cholesterole: HDL, LDL, and plasma trigliceige concentration, hepatic markers:

were followed at baseline, 8 weeks and 6 months: fasting glucose, insuline,

for extrapiramidal sindrome prophilaxy. The following metabolic parameters

Introduction

In the study there were included 19 adolescents aged 12–17 years old who were

diagnosed with early-onset and very-early-onset schizophrenia according to

DSM-IV criteria and KIDDIE-SADS scales. These patients were treated with

risperidone 2–4 mg/day for schizophrenia and trihexiphenidum (2–4 mg/day)

for extrapiramidal syndrome prophylaxis. The following metabolic parameters

were followed at baseline, 8 weeks and 6 months: fasting glucose, insuline, 

cholesterol: HDL, LDL, and plasma trigliceride concentration, hepatic markers:

ALT and AST as well as TSH and weight.

Results

At 8 weeks there were no consistent modifications in weight or metabolic

parameters but at the 6 months measurement 58% of the patients had gained more

than 5kg and there could be observed slight elevations in plasma trigliceride concentration and cholesterol levels.

Conclusions

The small number of patients is for clear a limitation, therefore we find that

studies on bigger populations are necessary. Nevertheless this results show the

need for a multidisciplinary – psychiatrist, endocrinologist, family doctor –

approach of patients undergoing antipsychotic treatment and especially during a

period marked by growth and change like adolescence.

DOI: 10.1530/endoabs.32.P731

P732

Metabolic side effects of second generation antipsychotic drugs in adolescents

Iuliana Dobrescu1,2, Florina Rud1,2, Gianina Cristina Anghel1,2,

Cristina Petrescu-Ghenea1 & Carmen Trutescu2

1Child and Adolescent Psychiatry Clinic, Prof. Dr Alexandru Obregia

Clinical Psychiatry Hospital, Bucharest, Romania; 2Child and Adolescent

Psychiatry Department, Carol Davila University of Medicine and Pharmacy,

Bucharest, Romania.

Introduction

Although for the last 2 decades we have witnessed a rise in the use of second

generation antipsychotic treatment in children and adolescents suffering from

psychiatric disorders we do not have enough studies in specialty literature to

estimate the risks associated with this medication. Recent data and also our

clinical experience shows that second generation antipsychotic drugs adminis-

tration correlates with considerable weight gain and also with altering of glucose,

lipide and other metabolic markers. The utility of antipsychotic treatment in

psychiatric disorders and schizophrenia is well known. But does it outweigh the

risks? Studies that evaluate the risk/benefit ratio of antipsychotic treatment in early-onset and very-early-onset schizophrenia are much needed.

Design/methods

In the study there were included 19 adolescents aged 12–17 years old who

were diagnosed with early-onset and very-early-onset schizophrenia according to

DSM-IV criteria and KIDDIE-SADS scales. These patients were treated with

risperidone 2–4 mg/day for schizophrenia and trihexiphenidum (2–4 mg/day)

for extrapiramidal syndrome prophylaxis. The following metabolic parameters

were followed at baseline, 8 weeks and 6 months: fasting glucose, insuline, 

cholesterol: HDL, LDL, and plasma trigliceride concentration, hepatic markers:

ALT and AST as well as TSH and weight.

Results

At 8 weeks there were no consistent modifications in weight or metabolic

parameters but at the 6 months measurement 58% of the patients had gained more

than 5kg and there could be observed slight elevations in plasma trigliceride concentration and cholesterol levels.

Conclusions

The small number of patients is for clear a limitation, therefore we find that

studies on bigger populations are necessary. Nevertheless this results show the

need for an multidisciplinary – psychiatrist, endocrinologist, family doctor –

approach of patients undergoing antipsychotic treatment and especially during a

period marked by growth and change like adolescence.

DOI: 10.1530/endoabs.32.P731

P733

Gastric banding vs gastric bypass: evolution of anthropometric parameters and related comorbidities during the 2 years after surgery

Ana Rita Caldas1, Ana Maia Silva1, Cláudia Amaral1, Cláudia Freitas1, André Couto Carvalho1, Isabel Silva1, Fernando Pichel1, Carla Silva1, Mário Marcos1, Jorge Santos1, Carlos Nogueira1 & Maria Helena Cardoso1

1Hospitalar do Porto, Porto, Portugal; 2Universidade Fernando Pessoa, 

Porto, Portugal.

Introduction

Bariatric surgery has proved to be effective in the management of morbid obesity. Our purpose was to compare the results obtained with adjustable gastric banding (GB) and Roux-en-Y Gastric Bypass (RYGB) during 2 years of follow-up after surgery, with regard to anthropometric parameters and related comorbidities.

Methods

We evaluated prospectively patients who underwent GB and RYGB between 2004 and 2010 and compared the evolution of anthropometric parameters, prevalence of type 2 diabetes mellitus (DM), hyperlipidemia and hypertension during 2 years of follow-up.

Results

109 patients were submitted to bariatric surgery: 51 patients to GB (mean age 48.4±10.6, 84.3% women) and 58 to RYGB (mean age 45.2±9.2, 86.2% women). There were no statistically significant differences between the two groups regarding age, gender, weight, BMI, weight excess, BMI excess and prevalence of DM and hypertension before surgery; hyperlipidemia was more frequent in the RYGB group (46.6 vs 27.5%). Two years after surgery, percentages of excess weight and BMI losses were higher with RYGB (70.9±14.0 vs 38.5±22.3% and 83.7±7.8 vs 45.6±26.3% respectively). In the GB group, DM remitted in 75% of the patients, hypertension in 61.1% and hyperlipidemia in 64.3%, in the RYGB group, the respective percentages were 65, 61.1 and 85.2%.

Patients who didn’t achieve resolution of their comorbidities improved and needed less medication. The reduction of the prevalence of DM, hypertension and hyperlipidemia was significant in both groups and the post-surgical prevalence of those comorbidities was not significantly different between GB and RYGB.

Conclusions

Our study shows that RYGB results in higher weight and BMI loss than GB until the second year after surgery. Both procedures allow a significant resolution of obesity-related comorbidities.

DOI: 10.1530/endoabs.32.P733

P734

Obesity-induced hepatic and placental inflammation are absent in obese gestating mice compared to control fed dams

Camilla Ingvorsen1, Anna Hammerich Thyssen1, Denise Fernandez-Twinn1, Susan Ozanne1, Susanne Brüix2 & Lars Hellgren1,2

1Technical University of Denmark, Kongens Lyngby, Denmark; 2Centre for Fetal Programming, Copenhagen, Denmark; 3University of Cambridge, Cambridge, UK.

Introduction

Maternal obesity is associated with increased risk of metabolic dysfunction in the offspring. It is not clear which physiological aspects of the obese state that cause this metabolic programming. Obesity causes many metabolic changes but also low grade inflammation. In this study, we have determined if increased low grade inflammation was present in obese dams compared to controls during gestation.

Methods

Female C57BL/6 mice were fed either a standard chow diet (3% fat) or a highly palatable obeseogenic diet consisting of a high fat pellet diet (20% fat) supplemented with sweetened condensed milk. After 6 weeks on the diets, half the mice (n = 12) were sacrificed and the remaining half were mated and sacrificed on gestation day 18 (n = 8). Blood and tissues were collected for analysis.

Results

The obeseogenic diet increased adiposity, adipocyte size and leptin levels both in the pre-gestating and gestating state. There was also a tendency for increased

Endocrine Abstracts (2013) Vol 32
hepatic lipid accumulation in obese mice. Body weight was increased in pre-gestating obese mice, but at the end of gestation there was no change in body weight between control and obese dams. Insulin levels were higher in pre-gestating obese dams. During gestation, a marked increase in the control dams, not seen in the obese, equalized this difference. Blood glucose levels were unaffected by diet or gestation. Local inflammation was assayed by macrophage count in liver and placenta. Hepatic macrophage count was in general reduced by gestation but only obese mice showed a significantly lower macrophage count during gestation, due to an elevated count prior to gestation. Placenta macrophage count was unaffected by the diet.

Conclusion
Obese dams were found not to express increased inflammation in placenta and liver compared to lean dams, despite profound hepatic inflammation before gestation. Thus, the diet-induced inflammation is not maintained during gestation.

DOI: 10.1530/endoabs.32.P734

P735
Serum IL18 concentration is associated with resting energy expenditure independently of BMI
Agnieszka Nikolajuk1,2, Agnieszka Adamska2, Monika Karczewska-Kupczewska2, Natalia Matulewicz2, Magdalena Stefanowicz2, Irina Kowalska1,2 & Marek Straczkowski1,2
1Department of Prophylaxis of Metabolic Diseases, Polish Academy of Sciences, Olsztyn, Poland; 2Department of Endocrinology, Diabetology and Internal Medicine, Medical University, Bialystok, Poland.

Introduction
Numerous studies indicate an association between low-grade chronic inflammation and predisposition to type 2 diabetes and atherosclerosis. IL-18 is a proinflammatory cytokine with proatherogenic properties. Existing evidence indicated that circulating IL-18 was associated with insulin resistance, metabolic syndrome and type 2 diabetes. Some data suggest that endogenous IL-18 signaling modulates food intake, metabolism and adiposity, as homeostatic regulator. The aim of the present study was to estimate the relationship between serum IL-18 concentration and resting energy expenditure (REE).

Methods
Our study involved 60 young (age: 23.43 ± 2.62 years), apparently healthy men with normal glucose tolerance. Anthropometric measurements, blood biochemical analysis, euglycemic hyperinsulinemic clamp and indirect calorimetry before and during the clamp were performed in the studied group.

Results
The serum concentrations of IL18 was 259.95 ± 98.36 pg/ml. We found that serum IL18 positively correlated with BMI (r = 0.26, P = 0.04), fasting serum insulin (r = 0.26, P = 0.047) and free fatty acids after the clamp (r = 0.50, P = 0.001). A significant association between basal and post-clamp REE with serum IL18 (r = 0.40, P = 0.001 and r = 0.26, P = 0.043, respectively) was observed in the studied group. In multiple regression analysis the relationship between IL18 and REE was independent of BMI (β = 0.22, P = 0.008).

Conclusion
Our data indicate that serum IL18 concentration is associated with resting energy expenditure independently of BMI.

DOI: 10.1530/endoabs.32.P735

P736
High fat diet induces site specific resistance to LPS-stimulated STAT3 activation in the CNS
Beatriz Borjes, Rodrigo Rorato, Ernane Uchoa, Paula Marango, Jose Antunes-Rodrigues & Lucia Elias
School of Medicine Of Ribeirao Preto, University of Sao Paulo, Ribeirao Preto, Sao Paulo, Brazil.

Hypophagia and increased energy expenditure under inflammatory condition, such as observed after bacterial lipopolysaccharide (LPS) administration, are associated with activation of JAK2–STAT3 signaling in the CNS. High fat diet (HFD) is known to induce hypothalamic resistance to leptin signaling mediated by JAK2–STAT3 pathway. In this study we investigated the expression of p-STAT3 in the hypothalamus and brainstem of HFD treated animals under LPS (100 μg/kg) stimulation. Wistar rats fed standard/low-fat diet (3.95 kcal/g) or HFD (6.3 kcal/g) for 8 weeks were assigned into control diet-saline, control diet-LPS, HFD-saline and HFD-LPS groups. LPS reduced feeding in the control diet, but not in the HFD group. In control diet fed rats, LPS increased the STAT3 phosphorylation in the arcuate nucleus and ventromedial hypothalamic nucleus, but not in the HFD group. HFD per se increased p-STAT3 in the ARC with no further activation after LPS. Differently to the hypothalamic response, LPS increased p-STAT3 in the nucleus of the solitary tract (NTS) and raphé pallidus both in control diet and HFD fed groups, although this response was lower in the latter group. Despite not affecting food intake, LPS decreased body weight in HFD rats, which was associated with increased number of Fos and Fos/TH neurons in the NTS, and HFD-LPS showed higher number of activated non-catecholaminergic and catecholaminergic neurons in the NTS, compared with control diet-LPS group. In conclusion, our data indicate that LPS activates STAT3 mediated pathway in the hypothalamus and brainstem, leading to hypophagia, however acute effects of LPS on food intake, but not body weight loss, in stabilized in HFD leptin resistant rats. Despite the absence of hypophagic effect, acute LPS under HFD induced body weight loss with higher brainstem neuron activation, suggesting that resistance to acute LPS effects under HFD might be selective to the hypothalamus.

DOI: 10.1530/endoabs.32.P736

P737
Association of mitochondrial respiratory chain polymorphisms with obesity and type 2 diabetes in the Spanish population
Griselda De Marco Solana1, María I. Mansego1, Monica Pineda-Alonso2, Gemma Rojo-Martínez3,4, María T. Martín-Larrad4, Sonsoles Morcillo4,5, María M Morales-Suárez-Varela6,7, Arturo Corbatón-Anduchel4,8, Antonio Duets-Laita9, Gracia M Martín-Núñez4,9, Juan C Martín Escudero10, Jose Redón10, Federico Sorgüer10, Rafael Carmenas10, Manuel Serrano-Rios4,5 & Feliciano Javier Chaves11
1Research Foundation of University Clinic Hospital–INCLIVA, Valencia, Spain; 2Rio Hortega University Hospital, Valladolid, Spain; 3Carlos Haya University Hospital, Málaga, Spain; 4CIBER of Diabetes and Associated Metabolic Diseases (CIBERDEM), Barcelona, Spain; 5Biomedical Research Foundation of the University Clinical Hospital San Carlos, Madrid, Spain; 6CIBER actions – Epidemiology and Public Health, Madrid, Spain; 7Center for Public Health Research (CSIP), University of Valencia, Valencia, Spain; 8University Clinic Hospital of Valencia, Valencia, Spain; 9Institute of Health Carlos III, Ministry of Health, Valencia, Spain.

Objective
To study the association between genes coding for mitochondrial respiratory chain (MRC) subunits and BMI and obesity as well as the impact on the risk to develop type 2 diabetes in the general population from Spain. Research design and methods
Three thousand seven hundred and thirty-one subjects (age range 21–89) from three different population-based studies of Spain, were studied. Forty-eight single nucleotide polymorphisms (SNPs) of mitochondrial genes which codify MRC proteins were selected and processed by the SNPlex method.

Results
Significant associations were observed between polymorphisms rs4600063 (SDHC gene), rs11205591 (NDUF55 gene), rs10891319 (SDHD gene) and BMI (P value = 0.04, 0.0011 and 0.0004 respectively) and obesity risk (OR = 0.72, P value = 0.0072; OR = 0.72, P = 0.039 and OR = 1.25, P = 0.0038 respectively). In addition, polymorphisms rs11205591 and rs10891319, showed a significant epistatic interaction for BMI levels and obesity risk. Finally, the GG genotype of rs11205591 polymorphism significantly reduced the risk of being diabetic after including age and sex as covariables (OR = 0.32, 0.17–0.62; P value = 0.0001), and BMI (OR = 0.37, 0.19–0.72; P value = 0.0008).

Conclusions
Polymorphisms of genes coding MRC can be involved in BMI variation and can be related to the risk for being obese in the Spanish general population. Furthermore, the rs11205591 (NDUF55 gene) polymorphism might contribute to the risk to develop type 2 diabetes.

DOI: 10.1530/endoabs.32.P737
**P738**

The FXR agonist obeticholic acid normalizes lipid droplet and triglyceride handling in visceral adipose tissue preadipocytes from a non-genomic rabbit model of metabolic syndrome

Elena Maneschi1, Linda Vignozzi1, Annamaria Morelli2, Tommaso Mello2, Sandra Filippi3, Ilaria Cellai4, Paolo Comiglio3, Erika Sarchielli3, Alessandra Calcagno3, Roberto Vettor3, Gabriella Barbara Vannelli2, Luciano Adorini4 & Mario Maggi1

1Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence, Italy; 2Department of Experimental and Clinical Medicine, University of Florence, Italy; 3NeuroFarba, University of Florence, Florence, Italy; 4Intercept Italia, Perugia, Italy; University of Padua, Padua, Italy.

Lever and visceral ectopic fatty tissue disposition is a major metabolic derangement leading to type 2 diabetes, hypertension, dyslipidaemia, recapitulated in the metabolic syndrome (MetS). We have demonstrated that the selective FXR agonist obeticholic acid (OCA, INT-747) ameliorates the metabolic profile and reduces visceral adipose tissue (VAT) in a high-fat diet (HFD)-induced rabbit model of MetS. We now report the effects of OCA treatment in HFD (0.5% cholesterol and 4% peanut oil) rabbits, and on the adipogenic capacity of isolated VAT rabbit preadipocytes (rPAD). VAT and liver were studied by immunohistochemistry, Western blot and RT-PCR. Isolated rPAD were exposed to adipocyte differentiating mixture (DIM) to evaluate their adipogenic ability. Adipocyte size, as well as expression of the anti-lipolytic protein perilipin-1 and cytosolic GLUT-4, indicating adipocyte dysfunction, were significantly increased in VAT of HFD compared to regular diet (RD) rabbits, and normalized by OCA treatment. TNFα expression, along with other steatosis (PPARγ and adiponectin) and inflammation (TNFα, IL6 and IL10) markers were also significantly increased in HFD liver and normalized by OCA treatment. Interestingly, rPAD from HFD-rabbits showed a reduced responsiveness to DIM, and in particular to insulin, as demonstrated by reduced triglyceride synthesis, decreased glucose uptake, and impaired lipid droplets fusion, as well as by the reduced induction of adipogenesis- and lipid droplet-handling specific genes. OCA treatment preserved all the DIM-induced adipocyte functions, normalizing the markedly increased lipid droplet size in HFD-derived adipocytes and the increased major lipid-fusion complex SNARE. In conclusion, OCA dosing in a MetS rabbit model positively affects liver and VAT functions, increasing their efficiency in triglyceride and lipid droplet handling. This could reflect the ability of OCA to restore insulin sensitivity in committed adipose tissue unable to finalize its storage function, thus counteracting MetS-induced metabolic alterations and pathological fatty tissue disposition.

DOI: 10.1530/endoabs.32.P738

**P739**

Corticotrophin realising factor affects the immune phenotype of adipocytes via CRF1 and CRF2 receptors

Eirini Dermitzaki, George Liatopoulos, Ariadni Androulidaki, Christos Tsatsanis & Andrew Margioris

School of Medicine, University of Crete, Heraklion, Crete, Greece.

Introduction

The corticotrophin-releasing factor (CRF) family of neuropeptides and their receptors affect innate immunity. A fully working peripheral CRF system is present in adipose tissue. In obesity, macrophages and adipocytes interact causing local and systemic inflammation. In addition, macrophages and adipocytes share common characteristics including production of inflammatory cytokines in response to lipopolysaccharides (LPS) via the toll-like receptor-4 (TLR4) which both macrophages and adipocytes express. Aim of this work was to examine the effects of CRF1 and CRF2 agonists and antagonists on the immune machinery of adipocytes.

Description of methods

We have used 3T3L1 mouse pre- and differentiated adipocytes. IL6/IL8 were measured by ELISA, the TLR4 receptor by RT-PCR and FACS analysis. Results

Our data are as follows: i) LPS induced TLR4 expression and the production of interleukins IL6 and IL8 by mature adipocytes but not by pre-adipocytes. ii) LPS induced the differentiation of pre-adipocytes to adipocytes. iii) pre-adipocytes and adipocytes expressed the CRF1 and CRF2 receptors. iv) CRF1 agonists decreased basal and LPS-induced differentiation of pre-adipocytes. v) CRF2 agonists transiently suppressed the expression (transcript and protein) of TLR4 as well as the production of interleukins by pre-adipocytes. vi) both CRF receptor agonists inhibited basal and LPS-induced expression of TLR4 as well as the production of interleukins and adipokines (adiponectin and leptin) in mature adipocytes.

Conclusion

Our results indicate that CRF neuropeptides suppress TLR4 expression in adipocytes via CRF2, an effect containing their pro-inflammatory activity. They also suppress the differentiation of pre-adipocytes exclusively via CRF1. Thus, CRF appears to exert an anti-inflammatory effect in adipocytes.

DOI: 10.1530/endoabs.32.P739

**P740**

Obese hypogonadal men treated with testosterone undecanoate injections up to 5 years substantially and progressively lose weight

Farid Saad1,2, Ahmad Haider3, Gheorge Doros4 & Abdulmaied Taish4

1Bayer Pharma AG, Berlin, Germany; 2Gulf Medical University School of Medicine, Ajman, United Arab Emirates; 3Private Urology Practice, Bremerhaven, Germany; 4Boston University School of Public Health, Boston, Massachusetts, USA; 5Boston University School of Medicine, Boston, Massachusetts, USA.

Introduction

Abdominal adipose tissue suppresses testosterone production by various mechanisms affecting the hypothalamic–pituitary–gonadal axis. Hypogonadism leads to further accumulation of fat mass thus creating a vicious circle. This study analysed the effects of restoring testosterone in obese hypogonadal men.

Methods

Cumulative, prospective, registry study of 181 men (mean age: 59.11 ± 6.06 years) with testosterone levels below 12.1 nmol/l and a BMI of ≥ 30 kg/m². All men received parenteral testosterone undecanoate 1000 mg/12 weeks following an initial 6-week interval. 89 men were treated 5 years, 114 4 years, 133 3 years, 152 2 years, and 81 1 year. Changes in anthropometry and metabolic parameters are a result of the design as new patients are added once they have received at least 1 year of treatment.

Results

At the end of the observation period, mean weight (kg) decreased from 114.71 ± 11.59 (minimum 87.0, maximum 139.00) to 93.24 ± 8.49 (minimum 80.0, maximum 115.0). This decrease was statistically significant vs baseline (P < 0.0001) and each year compared to previous year (P<0.0001). Mean change from baseline was -16.41 ± 0.3%. After 5 years, all men had lost any weight, 99% had lost ≥ 5 kg, 90% ≥ 10 kg, 70% ≥ 15 kg, and 40% ≥ 20 kg. Waist circumference (cm) as a measure of abdominal fat decreased from 111.2 ± 7.54 (min 89.00; max 129.00) to 100.47 ± 7.11 (min 84.00; max 117.00), BMI from 36.72 ± 3.72 (min 30.10; max 46.51) to 30.22 ± 2.6 (min 25.66; max 36.71). Fasting glucose decreased from 5.84 ± 0.84 to 5.41 ± 0.12 mmol/l, total cholesterol from 7.63 ± 0.95 to 4.97 ± 0.28, LDL from 4.47 ± 1.03 to 2.94 ± 0.93, triglycerides from 3.31 ± 0.56 to 2.17 ± 0.13 mmol/l, Systolic blood pressure decreased from 159.17 ± 15.9 to 139.08 ± 10.99 mmHg, diastolic blood pressure from 96.5 ± 11.01 to 80.39 ± 7.51 mmHg (P<0.0001 for all).

Conclusion

Normalising testosterone produced loss of weight/waist circumference and improved metabolic profile. These improvements were progressive over 5 years.

DOI: 10.1530/endoabs.32.P740

**P741**

Consumption of low-carbohydrate/high fat diets impairs glucose tolerance in rats independent of changes in body composition

Maximilian Bielohuby, Ayse Zengin, Amon Horngacher, Sarina Meurer & Martin Billigmaier

Endocrine Research Unit, Medizinische Klinik und Poliklinik IV, Klinikum der LMU, Munich, Germany.

Moderate, ‘Atkin’s-style’ low-carbohydrate/high fat diets (LC-HFD) are claimed to induce weight loss in overweight subjects and to ameliorate glucose metabolism, whereas extreme ketogenic LC-HFD are used to treat neurological disorders like pediatric epilepsy. To investigate the effects of both types of LC-HFD on glucose and insulin metabolism independent of the energetic intake, we pair-fed male Wistar rats isoorientic of standard rodent chow (CH) or one of

Endocrine Abstracts (2013) Vol 32
two different LC-HF diets (percentage of metabolizable energy, fat/protein/CHO: LC-HF-1 (78.7/19.1/2.2), LC-HF-2 (92.8/5.1/2.7) and CH (36.7/19.6/4.3)) for 4 weeks. Since we had previously observed increased visceral fat accumulation in rats pair-fed the LC-HFD, we also studied rats in which the fat mass was clamped to the control group by restricting LC-HFD intake to 80% of caloric intake of the control group. In pair-fed groups, rats on LC-HFD displayed significantly higher fat mass when compared to CH (P < 0.01). Furthermore, dynamic challenge tests (oGTT, i.p.GTT, insulin tolerance tests and hyperinsulinemic-euglycemic clamp) revealed that rats pair-fed the LC-HF diets have impaired glucose tolerance. As expected, the reduction of LC-HFD intake to only 80% equalized the fat mass between LC-HFD groups and controls. The restriction of LC-HFD intake to 80% improved glucose tolerance during oGTT compared to rats which were regularly pair-fed with LC-HFD. However, glucose tolerance was still impaired when compared to rats fed the standard control diet (AUC of glucose during oGTT: Chow: 12 986 ± 801; LC-HF-1 (80%): 16 662 ± 1111; LC-HF-2 (80%): 23 809 ± 1485; CH vs LC-HF-1 (80%): P = 0.007; CH vs LC-HF-2 (80%): P < 0.001). In summary, these data clearly argue against a beneficial effect of LC-HFD on glucose and insulin metabolism. Impaired glucose tolerance occurred with LC-HFD independent of the relative abundance of fat and protein and in the absence, energy overconsumption and increased fat mass.

**Introduction**

Various hypothesis exist about the mechanism of changes in glucose control and insulin sensitivity after bariatric surgery.

**Description of methods/design**

The aim of our study was to determine glucose, insulin, C-peptide and GLP-1 levels after test meal (Fresubin drink a 200 ml given at 0 min; 200 kcal, 15% protein, 30% fat and 55% carbohydrate) before and 5 days after gastric bypass surgery in a 22 obese patients (age: 36.22 ± 12.66; BMI: 44.60 ± 4.31 kg/m²). Glycaemia (mmol/l; glucose oxidase), insulin (ECLA, Roche Diagnostics, pmol/l), C-peptide (ECLA, Roche Diagnostics, pmol/l) and GLP-1 (active 7–36) (pM/l; ELISA, ALPCO Diagnostics) were determined in two separate days in 0, 15, 30, 45, 60, 90 and 120 min.

**Results**

There were no significant difference between areas under the glucose curve (X ± s.d.): (645.562 ± 20.545 vs 621.600 ± 24.07 mmol/l per min; P = 0.304) and under the C-Peptide curve (293 074.125 ± 23 539.973 vs 267 750.375 ± 19 685.499 pmol/l per min; P = 0.317) while there was significantly lower area under the insulin curve in day 5 (38 263.075 ± 6079.309 vs 23 539.875 ± 2571.388 pmol/l per min; P = 0.032). There was significant increase in area under the GLP-1 curve in day 5 (163.00 ± 73.61 vs 861.94 ± 251.22 pmol/l per min; P < 0.05).

**Conclusion**

In conclusion, insulin response after test meal is significantly decreased after gastric bypass surgery after 5 days without significant difference in glucose response, indicating early improvement in insulin sensitivity. The significant improvement in GLP-1 response after test meal among patients after gastric bypass surgery may be responsible for the metabolic effects of bariatric surgery, especially on glucose homeostasis.

**DOI:** 10.1530/endoabs.32.P743

---

**P743 Early changes in glucose, insulin, C-peptide and GLP-1 levels after test meal in obese patients after gastric bypass surgery**

Dragana Micic, Marija Dzajic, Nenad Babic, Sinisa Sunac-Dumanovic, Goran Cvijovic, Svetlana Ignjatovic, Marijana Dajak, Dusan Micic, Danica Pejovic, Jelena Milin & Danko Jeremic

Clinical Center of Serbia, Belgrade, Serbia.

**Results**

Eight Wistar rats were treated with T1AM for five days (10 mg/kg per day by i.p. injection). The rats were sacrificed by guillotine and tissue samples were immediately removed and frozen in liquid nitrogen. Gene expression was evaluated by two-colour microarray analysis, using the whole rat genome G4131F microarrays (Agilent Technologies, Palo Alto, CA, USA). Significant differences in gene expression were confirmed by quantitative PCR.

In adipose tissue we detected 378 differentially expressed genes (DEGs), 268 up-regulated and 110 down-regulated, while in liver DEGs were 114 (63 up-regulated and 51 down-regulated). Functional analysis of microarray results revealed interesting interplays among DEGs. In adipose tissue pathway analysis provided evidence of decreased adipogenesis and stimulated lipolysis and fatty acid catabolism; modulated genes included acyl-CoA synthase 5, peroxisomal biogenesis factor 5, sirtuin 2, CCAAT/enhancer binding protein β (C/EBPβ) and the adiponectin receptor PAQR3. In liver most of the differentially expressed genes were of unknown function but glycerol kinase and malic enzyme were inhibited.

We conclude that in vivo T1AM administration produced significant transcriptional effects, which are expected to stimulate lipid catabolism and induce a reduction of fatty mass. These actions might therefore provide the basis for the reported effectiveness of T1AM as a lipolytic agent.

**DOI:** 10.1530/endoabs.32.P744

---

**P742 Depression and suicidal ideation among adults with metabolic syndrome: data from the 2008–2010 Korea national health and nutrition examination survey**

Jun Goo Kang, Sung Hoon Yu, Chul Sik Kim, Seong Jin Lee, Sung-Hee Ihm, Yoo-Cheol Hwang, Hong Yup Ahn & Cheol-Young Park

1Hallym University College of Medicine, Seoul, Republic of Korea; 2Kyung Hee University Hospital at Gangdong, Seoul, Republic of Korea; 3Dongguk University-Seoul, Seoul, Republic of Korea; 4School of Medicine Sungkyunkwan University, Seoul, Republic of Korea.

**Aim**

Suicide and depression are one of the highest public health problems worldwide. Suicidal ideation represents an important phase in the suicidal process and often precedes suicidal attempts or completed suicide. Patients with chronic medical disease are more likely to report suicidal thoughts and depression. However the studies on relationship between these conditions and metabolic syndrome are rare. We aimed at investigating the prevalence of depression and suicidal ideation among adults with metabolic syndrome in Korea.

**Methods**

We analyzed data for 17 924 persons (men 7516 persons and women 10 408 persons) from 2008–2010 KNHANES who did not have cancer or hepatitis or liver cirrhosis. Each individual was assessed for the presence of metabolic syndrome according to the NECP-ATPIII criteria except for waist circumference, for which new criteria recently suggested by Korean Society for Study of the Obesity was used. The presence of depression or suicidal ideation and were defined by a self-reported questionnaire asking if the participants had ever been diagnosed with depression by medical doctor or had any suicidal thoughts. Results

The prevalence of depression (17 vs 14%, P < 0.001) and suicidal ideation (20 vs 17%, P < 0.001) was significantly higher in participants with metabolic syndrome. Mean scores for the EQ-5D decreased significantly with participants with depression (0.80 ± 0.22 vs 0.91 ± 0.13, P < 0.001) and suicidal ideation (0.79 ± 0.22 vs 0.92 ± 0.13, P < 0.001) in the group with metabolic syndrome.

**Conclusions**

This study shows that metabolic syndrome is associated with depression and suicidal ideation and this relationship was negatively associated with health related quality of life.

**DOI:** 10.1530/endoabs.32.P742

---

**P744 Modulation of gene expression by 3-lodothyronamine: evidence of a lipolytic pattern**

Veronica Mariotti, Caterina Ioffrida, Erika Melissari, Manuela Di Russo, Sabina Frascarelli, Silvia Pellegrini & Riccardo Zucchi

University of Pisa, Pisa, Italy.

3-lodothyronamine (T1AM) is a recently discovered compound which can be regarded as a novel hormone, since it is an endogenous relative of thyroid hormone with systemic distribution, which does not interact with thyroid hormone receptors, but rather with specific G protein-coupled receptors. T1AM has been reported to modulate energy metabolism, and in rodents chronic T1AM treatment has been associated with lipolysis and decreased body weight. To investigate the mechanism of this action we determined the effects of in vivo T1AM administration on gene expression in rat adipose tissue and liver.

Eight Wistar rats were treated with T1AM for five days (10 mg/kg per day by i.p. injection). The rats were sacrificed by guillotine and tissue samples were immediately removed and frozen in liquid nitrogen. Gene expression was evaluated by two-colour microarray analysis, using the whole rat genome G4131F microarrays (Agilent Technologies, Palo Alto, CA, USA).

Significant differences in gene expression were confirmed by quantitative PCR.

In adipose tissue we detected 378 differentially expressed genes (DEGs), 268 up-regulated and 110 down-regulated, while in liver DEGs were 114 (63 up-regulated and 51 down-regulated). Functional analysis of microarray results revealed interesting interplays among DEGs. In adipose tissue pathway analysis provided evidence of decreased adipogenesis and stimulated lipolysis and fatty acid catabolism; modulated genes included acyl-CoA synthase 5, peroxisomal biogenesis factor 5, sirtuin 2, CCAAT/enhancer binding protein β (C/EBPβ) and the adiponectin receptor PAQR3. In liver most of the differentially expressed genes were of unknown function but glycerol kinase and malic enzyme were inhibited.

We conclude that in vivo T1AM administration produced significant transcriptional effects, which are expected to stimulate lipid catabolism and induce a reduction of fatty mass. These actions might therefore provide the basis for the reported effectiveness of T1AM as a lipolytic agent.

**DOI:** 10.1530/endoabs.32.P744

---

**Endocrine Abstracts (2013) Vol 32**
**P745**

Evaluation of gastric bypass effect on cardiovascular risk and quality of life in our area

Isabel Mateo-Gavira, Pilar Roldán-Caballero, Francisco Javier Vílchez-López, Laura Larrín-Escandon, Julián Tamayo-Serrato, María Belén Ojeda-Schuldt, Immaculada Gavilán-Villarejo & Manuel Aguilar-Diosdado

Endocrinology Department, University Hospital Puerta del Mar, Cádiz, Spain.

Objectives

i) To determine the prevalence of major comorbidities of morbid obese, ii) to evaluate the gastric bypass effect on this comorbidities, on the 10 years estimated cardiovascular risk and iii) To assess the impact of bariatric surgery on the quality of life in these patients.

Methods

Cohort study with insubject measures (before–after) in a sample of patients with morbid obesity who underwent gastric bypass. Demographic characteristics, anthropometric parameters, cardiovascular risk factors and surgical complications were analyzed. The estimation of cardiovascular disease risk at 10 years was determined according to the Framingham Risk Score and the impact on the quality of life using the BAROS test (Bariatric Analysis and Reporting Outcome System).

Results

162 patients were included (74.3% females), with mean age 38.87 ± 10.11 years and BMI before surgery 51.12 ± 7.22 kg/m². Two years after surgery the percentage of weight lost was 72.85%. Four months after the bypass only 12 of the 41 patients with type 2 diabetes maintained the diagnosis of diabetes. Two years after surgery, the resolution of hypertension, dyslipidemia and diabetes occurred in 71.93, 92.7, and 92.68% cases respectively (P < 0.001). According to the Framingham Risk Score, 22.7% presented with a risk greater than 10% before surgery. Mean risk decreased from 5.82% at baseline to 2.21% 2 years after surgery (P < 0.001). 14.9% of patients had early complications and 27.2% developed later complications (the most frequent eventation). BAROS scale was excellent in 36.8% of cases, very good in 36.7% and good in 21.1% at 2 years.

Conclusions

Gastric bypass is an effective tool in weight loss, early beneficial effects on metabolic disorders, reduction in cardiovascular risk and improvement quality of life in morbid obese patients in our area.

DOI: 10.1530/endoabs.32.P745

**P746**

Green tea catechins attenuate high-fat diet effects related to obesity and diabetes without effect hypothalamic expression of TLR4 pathway or serotoninergic 1B and 2C receptors

Marcos Hiromu Okuda, Aline Alves de Santana, Mayara Franzoi Moreno, Bruno dos Santos, Mayara Moreno & Claudia Oller do Nascimento

Universidade Federal de São Paulo, São Paulo, Brazil.

Many mechanisms are proposed for green tea’s role as anti-obesity and anti-diabetic natural product. Two of them involve the hypothalamic control of energy balance: i) high-fat diets (HFD) rich in saturated fats induce low-grade inflammation, leading to leptin and insulin resistance; ii) serotonin receptors (5R) 1B and 2C activation have anorexigenic effects, 5R2C activation improves metabolic balance: i) high-fat diets (HFD) rich in saturated fats induce low-grade inflammation, leading to leptin and insulin resistance. Besides, we investigated whether these metabolic events were related to the hypothalamic inflammatory pathway (TLR4) and/or serotoninergic system (5R1B and 5R2C). H mice presented increased GTT area under curve and higher fat pads (sum of epididymal, retroperitoneal and mesenteric). Green tea catechins attenuated the increased GTT area under curve (F = 9.3 (3.37); P = 0.08 H vs HE) without effects on fat pads (F = 7.9 (3.86); P < 0.05 vs C). Fasting serum glucose, total cholesterol, and triglycerides were not different among groups. H mice presented lower HDL-cholesterol (F = 7.9 (3.31); P < 0.05 vs C, E, and HE), higher HOMA-IR (F = 9.3 (3.27); P < 0.05 vs C), and higher insulin (F = 7.2 (1.43); P < 0.05 vs C), which were improved by green tea catechins. Expression of TLR4 pathway proteins, 5R1B and 5R2C in the hypothalamus was not different among treatments. In conclusion, green tea catechins prevented some of the peripheral negative effects of HFD, which were not related to the expression of analyzed hypothalamic proteins. Whether other proteins of the inflammatory pathway or serotoninergic system are involved is to be investigated.

DOI: 10.1530/endoabs.32.P746

**P747**

Short-term ovariectomy did not cause tissue proinflammatory state, but associated with hyperlipidic diet caused hyperleptinemia and increased body weight gain

Maria Elizabethe de Sousa Rodrigues, Nelson Inacio Pinto Neto, Lila Missaé Oyama, Marcos Hiromu Okuda, Ana Claudia Hachul, Bruno dos Santos, Mayara Moreno & Claudia Oller do Nascimento

Universidade Federal de São Paulo, São Paulo, Brazil.

Obesity leads to low-grade inflammation, and high-fat diet is one of the major causes. On the other hand, menopause can aggravate it by promoting food intake alterations, and metabolic and endocrine adaptations. Thus, we used ovariectomized rats fed with high-fat diet to evaluate changes on the tissue inflammatory state. Forty days-old female Wistar rats were fed with: a hyperlipidic diet enriched with lard – H group; or chow diet – C group; for 30 days. After this period, the H and C were divided in four groups: sham-operated (SH and SC), ovariectomized (OVXH and OVXC). The respective diets were maintained, and 30 days after the surgery, the animals were euthanized. Serum, mesenteric adipose tissue, gastrocnemius muscle and liver were collected. Tissues IL10, TNFα and IL6 level, body weight gain, serum lipid profile, leptin and insulin were determined. MANOVA was used for statistical analysis, with Scheffe’s post-hoc test and P < 0.05. All parameters analysed were similar between SC and OVXC groups. The OVXH had higher mesenteric adipose tissue weight than SH (F = 4.9 (3.27); P < 0.05). The high-fat diet caused a decrease in IL10, IL6 and TNFα in mesenteric adipose tissue from SH and OVX rats compared to control diet. The association between hyperlipidic diet and ovariectomy promoted an increase in total body weight gain (F = 8.5 (3.27); P < 0.05) and serum leptin (F = 8.3 (3.27); P < 0.05) level in relation to others groups. These results demonstrate that 30 days of ovariectomy did not affect the analysed parameters. However, hyperlipidic diet associated to ovariectomy increases body weight gain and leptinemia. These results suggest that short period without oestrogen was not able to promote proinflammatory state in the assessed tissues, also that the hyperlipidic diet could potentiate the effects of ovariectomy on obesity development with hyperleptinemia.

DOI: 10.1530/endoabs.32.P747

**P748**

Differences among clinical, analytical and psychological outcomes among patients with an eating disorder after bariatric surgery

Joana Nicolau, Luisa Ayala, Rosmeri Rivera, Aleksandra Sperranskaya, Joselinha Oliveira, Apolonia Gil, Maria Puga, Regina Fortuny & Lluís Masmiquel

Hospital Son Llàtzer, Palma, Baleares, Spain.

Introduction

Information regarding eating disorders (ED) in postsurgical outcomes after bariatric surgery (BS) is scarce.

Objectives

To analyze the effect of BS on ED and to investigate if ED influence clinical, biochemical or psychological outcomes.

Methods

Sixty patients (78.3%, age 46.35 ± 9.89, months since BS 46.28 ± 28.1) who underwent BS, with a minimum follow up of 12 months, were evaluated cross-sectionally. Initial and current BMI, depressive symptoms, comorbidity, sociodemographic and biochemical parameters were recorded. For the screening

Endocrine Abstracts (2013) Vol 32
of ED, QWEP-R was administered.

Results
Before BS, five subjects were diagnosed of ED, two binge eating disorders (BED), one bulimia nervosa (BN) and one eating disorder non otherwise specified (EDNOS). After BS, BED resolved in all patients, BN persisted and EDNOS progressed to BN. Furthermore, after BS, 13 new cases of BED (21.6%) and six cases of BN (10%) were detected. Time from surgery was higher among BED patients (61.6 ± 23.47 vs 38.8 ± 26.44 months; P = 0.022). Furthermore, in these patients a greater proportion of calories obtained from alcohol intake (3.61 ± 6 vs 0.65 ± 1.74%; P = 0.041), a more prevalent history of prebariatric psychiatric disorders (85 vs 51.2%; P = 0.034) and a higher proportion of subjects who regained weight (61.5 vs 26.8%; P = 0.024) was observed. BN subjects had greater depression scores (17.4 ± 8.1 ± 5; P = 0.04). Both entities had more episodes of vomiting (61.5 vs 29.3%; P = 0.048 and 83.3 vs 61.5%; P = 0.047). Subjects with ED had more difficulties in following visits after BS (19.5 vs 53.8%; P = 0.028 and 19.5 vs 66.7%; P = 0.01).

Conclusions
Development of ED is frequent after BS. Owing to its potential association with weight regain, systematic screening of ED after BS is warranted.

DOI: 10.1530/endoabs.32.P748

P749

BMI as a prognostic feature in patients with breast cancer treated with chemo/endocrine therapy
Darko Katalinic1, Fedor Santek1, Antonio Juretic1, Martina Basic-Koretic1, Kresimir Loncar1, Majana Soce1, Nora Nikolac1,2 & Stjepko Plestina1
1University Hospital Centre Rebro-Zagreb, Zagreb, Croatia; 2University Hospital Centre Sisters of Charity, Zagreb, Croatia.

Introduction
High BMI has been associated with an increased risk for breast cancer among premenopausal and postmenopausal women. Several biological mechanisms play a significant role in the genesis and progression of breast cancer.

Material and methods
This study aimed to investigate relationship between BMI and breast cancer diagnosis or progression in a Croatian population. BMI, presence or absence of breast cancer and its clinical-pathological characteristics were analyzed in a series of 110 breast cancer women and compared with those of 110 healthy women prospectively.

Results
BMI was significantly associated with a larger-tumour size (BMI ≥ 30 respect to normal weight, P = 0.0001), and a higher probability of having positive axillary lymph node (P = 0.0001). In all BMI classes, there was a dose-dependent association between the amount of tobacco smoked daily and the prevalence of MetS. Compared to non-smokers, current smokers had lower levels of HDL cholesterol, and higher levels of triglycerides and waist circumference in all BMI-classes (all P < 0.0001). Smoking had no consistent association with blood pressure or fasting blood glucose levels. We observed a dose-dependent association between the amount of tobacco smoked daily and lower HDL cholesterol and higher triglyceride levels in normal weight, overweight and obese smokers (all P < 0.0001).

Conclusions
Smoking is associated with an increased risk for the metabolic syndrome, in all BMI classes. This increased risk was mainly related to lower levels of HDL cholesterol, and increased triglycerides and waist circumference.

DOI: 10.1530/endoabs.32.P750

P751

Associations between smoking and components of the metabolic syndrome
Sandra Slagger, Jana van Vliet-Oostapthouk, Judith Vonk, Marike Boezen, André van Beek & Melanie van der Klauw, Bruce Wolfenbuttel University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.

Background
The clustering of metabolic and cardiovascular risk factors is known as the metabolic syndrome (MetS). Lifestyle factors like smoking may contribute to the differences in prevalence of the MetS. The aim of this study was to examine the association between smoking and the MetS and its components in different BMI classes.

Methods
The present cross-sectional evaluation comprised 24,762 men and 35,558 women, participating in the LifeLines Cohort Study, of whom 6,058 and 7,469 were current smokers. MetS was defined using the criteria of the NCEP ATP III. Participants were categorized in different BMI classes (i) BMI ≥ 25; ii) BMI 25–30; iii) BMI > 30 kg/m²). Linear regression was used to test the association between smoking and the components of MetS, stratified by gender and age.

Results
There was an increasing prevalence of MetS with increasing BMI. In obese men (BMI ≥ 30 kg/m²) 62% fulfilled the MetS criteria, for women this was 41%. Overall, current smoking was associated with increased risk for MetS in both genders and all BMI classes (OR’s 1.7–2.4 for men, 1.8–2.5 for women, all P < 0.001). In all BMI classes, there was a dose-dependent association between the amount of tobacco smoked daily and the prevalence of MetS. Compared to non-smokers, current smokers had lower levels of HDL cholesterol, and higher levels of triglycerides and waist circumference in all BMI-classes (all P < 0.0001). Smoking had no consistent association with blood pressure or fasting blood glucose levels. We observed a dose-dependent association between the amount of tobacco smoked daily and lower HDL cholesterol and higher triglyceride levels in normal weight, overweight and obese smokers (all P < 0.0001).

Conclusions
Smoking is associated with an increased risk for the metabolic syndrome, in all BMI classes. This increased risk was mainly related to lower levels of HDL cholesterol, and increased triglycerides and waist circumference.

DOI: 10.1530/endoabs.32.P751

Endocrine Abstracts (2013) Vol 32
P752
Monocyte chemottractant protein-1 is associated with apolipoprotein A-1 and apolipoprotein e levels in obese premenopausal women
José Silva-Nunes1,2, Zulima Peeraly2, Nuno Pedrosotro, Ana Oliveira3, Leom Duarte1, Miguel Brito1 & Luisa Veiga1
1Endocrinology Department, Curry Cabral Hospital, CHLC, Lisbon, Portugal; 2Portuguese Diabetes Association, Lisbon, Portugal; 3Faculty of Health’s Technology, Lisbon Polytechnic Institute, Lisbon, Portugal;

Background
Obesity represents a cardiovascular risk factor. Monocyte chemoattractant protein-1 (MCP-1) is a known regulator of monocyte recruitment to sites of inflammation, and participates at the early phases of atherogenesis. Apolipoproteins, as part of the lipoprotein particles, are classically coupled with cardiovascular risk distinction.

Aims
To assess the association of anthropometric parameters, insulin resistance and MCP-1 levels with classic lipid and apolipoprotein profile, in both obese and normal-weight premenopausal women.

Methods
We studied 72 obese (age = 34.6 ± 7.8 years, BMI = 44.4 ± 8.5 kg/m², waist circumference = 118.6 ± 15.1 cm) and 73 normal-weight pre-menopausal women (age = 33.6 ± 8.4 years, BMI = 21.4 ± 1.7 kg/m², waist circumference = 71.5 ± 5.8 cm). Women were characterized for anthropometrics and a fasting blood sample was collected for MCP-1, insulin, glucose, total, LDL and HDL cholesterol, triglycerides, free fatty acids and apolipoproteins A-I, A-II, B, C-III, C-IV and E; insulin resistance was assessed by the homeostatic model assessment (HOMA-IR). We compared biochemical parameters between groups. In each group, we looked for correlations of lipid/apoprotein profile with MCP-1, insulin resistance and anthropometrics.

Results
Obese women presented significantly higher triglycerides (P < 0.001) and MCP-1 levels (P = 0.001) and significantly lower levels of HDL-cholesterol (P < 0.001) and apolipoprotein A-I (P < 0.001); we also found a trend for lower apolipoprotein A-II (P = 0.07). In the obese group (but not in the non-obese), MCP-1 was directly correlated with apolipoprotein E (P = 0.007; r = 0.35) and inversely associated with HDL-cholesterol (P = 0.013; r = 0.321) and apolipoprotein A-I (P = 0.021; r = 0.3). HOMA-IR was inversely associated with HDL-cholesterol (P = 0.032; r = 0.252) and directly associated with triglycerides (P = 0.003; r = 0.344). MCP-1 was not correlated with anthropometrics or HOMA-IR.

Conclusions
The higher levels of MCP-1 and triglycerides and low levels of HDL-cholesterol/apolipoprotein A-I observed in the obese women are consistent with a higher atherosclerotic activity. The association of MCP-1 levels with apolipoproteins A-I and E in obese women, independently from anthropometrics or insulin resistance, may indicate a way of regulation of the atherosclerotic activity in obesity.

DOI: 10.1530/endoabs.32.P752

P754
Apelin levels in men with metabolic syndrome with or without late-onset hypogonadism
Petya Angelova1, Zdravko Kamenov1 & Adelina Tsakova2
1Clinic of Endocrinology, Alexandrovska University Hospital, Medical University of Sofia, Sofia, Bulgaria; 2Central Clinical Laboratory, Alexandrovska University Hospital, Medical University of Sofia, Sofia, Bulgaria.

Apelin is a new adipokine associated with obesity. Data about the relationship of apelin to the metabolic syndrome (MS) are still scarce. Late-onset hypogonadism (LOH) is common in men with MS, but we did not find data about the levels of apelin in men with LOH.

The aim of this study was to determine the levels of apelin in men with MS with or without LOH.

Patients and methods
Ninety nine men were included in the study. Of them 65 had MS (IDF 2005) and they were devised according to their morning total testosterone (TT) level (cutoff 10.4 nmol/l) into two groups: MS-LOH (n = 21) and MS-NoLOH (n = 44). The control group consisted of 34 men without MS and LOH. Apelin was determined in serum using enzyme-linked immunosorbent assay.

Results
MS men were at mean age (± s.o.): 50.4 ± 9.6 years; BMI: 33.3 ± 7.7 kg/m², waist circumference (WC) = 111.7 ± 13.9 cm and TT = 15.6 ± 5.4 nmol/l. The control group was at age: 51.5 ± 6.4 years (NS); BMI: 23.7 ± 2.4 kg/m² (P < 0.001); WC = 89.8 ± 8.2 cm (P < 0.001) and TT = 17.9 ± 5.6 nmol/l (P < 0.001). MS-LOH sub-group had age 47.9 ± 10.5 years; BMI: 36.4 ± 9.5 kg/m²; WC = 114.6 ± 16.7 cm; TT = 8.1 ± 1.5 nmol/l and MS-NoLOH sub-group – age 51.6 ± 9.1 years (NS); BMI: 31.8 ± 6.3 kg/m² (P > 0.05); WC = 110.4 ± 12.5 cm (NS); TT = 16.3 ± 4.5 nmol/l (P > 0.001). The levels of apelin were higher in the MS group – 1.61 ± 0.53 ng/ml compared to the control one – 1.38 ± 0.57 ng/ml (P < 0.05). There was no difference between MS-LOH – 1.53 ± 0.52 ng/ml and MS-NoLOH – 1.65 ± 0.53 ng/ml sub-groups. The MS-NoLOH differed from the control group (P < 0.05).

Conclusions
In this study higher apelin levels were found in the presence of MS compared to healthy men, but did not differ between men having MS with or without LOH.

DOI: 10.1530/endoabs.32.P754

P755
Apnoic episodes impair insulin resistance independently of oxygen desaturations: evidence from morbid obese patients with discordant apnoea/desaturation indexes
Patricia Andráda, Ana Chacon, Eider Pascual, Camilo Silva, Jorge Iriarte, Maria J Gil, Pedro Pujante, Cristina Abreu, Javier Escalada, Gemma Frühbeck & Javier Salvador
University Clinic of Navarra, Pamplona, Spain.

Morbid obesity (MO) is often complicated by obstructive sleep apnoea (OSA), which in some cases is evaluated by polysomnigraphy. This cross-sectional study was designed to investigate the prevalence of discordance between desaturation index (DI) and apnoea-hypopnoea index (AHI) and its effects on insulin resistance and secretion in MO patients candidate to bariatric surgery (n = 496) in whom a full polysomnographic study was carried out. We identified 163 (33%) out of 496 patients with normal DI (< 3/h), 42 (26%) of which showed significant nocturnal apnoeas (AHI > 10). When comparing DI less than three patients with IAH > 10 (n = 42) with those showing IAH < 10 (n = 121), apnoea subjects showed higher fasting insulin (17.4 ± 1.1 vs 15 ± 0.6 µmol/l, P < 0.05), post-OGTT insulin peak (151.2 ± 11.5 vs 123.2 ± 5.6 µU/I, P < 0.05) and HOMA values (4.4 ± 0.3 vs 3.6 ± 0.1, P < 0.05) than those with AHI < 10, despite exhibiting similar waist and neck circumference. On the other hand, there were 333 patients with DI > 3, of which 60 (18%) showed AHI < 10. In this subgroup of patients with significant
oxygen desaturations there were no differences in fasting, post OGTT insulin levels or HOMA\textsuperscript{r} between patients classified according with AHI values. No differences were seen in insulinogenic index between patients with AHI > 10 and AHI < 10 in any of DI subgroups. AHI values were correlated with peak insulin values after OGTT (r = 0.15, P < 0.01). QUICKI (r = -0.17, P < 0.01), HOMA\textsuperscript{r} (r = 0.14, P < 0.05) and Matsuda index (r = -0.10, P < 0.01) only in patients with DI > 3. These findings support the blood sugar values pressure relations, suggesting that apnoeic episodes, independently of oxygen desaturations, participate in the impairment of carbohydrate metabolism seen in MO patients.

DOI: 10.1530/endoabs.32.P755

P756
Circulating endocannabinoids are differentially modulated during the oral glucose tolerance test
Flaminia Fanelli, Silvia Garelli, Marco Mezzullo, Guido Di Dalmazi, Federico Ponti, Jacopo Manzo, Elisa Dalla Benetta, Alberto Bazzocchi, Valentina Vicennati, Giuseppe Battista, Renato Pasquali & Uberto Pagotto
S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Emilia-Romagna, Italy.

The endocannabinoid system (ECS) is involved in the regulation of food intake and energy expenditure. Increased level of EC lipid mediators anandamide (AEA) and 2-acetyl-5-chloromethylgluceral (2AG) and/or a higher expression of cannabinoid receptor type 1 in central and peripheral districts are supposed to contribute to the development and maintenance of obesity and related dismetabolism. To understand the ECS response to insulin signal and to anthropometric and biochemical parameters, we evaluated the effect of an OGTT on circulating ECs in five fasted obese females (age: 41.4 ± 3.6 years, BMI: 32.5 ± 2.2 kg/m\textsuperscript{2}, waist circumference: 103.2 ± 11.1 cm). Blood samples were collected before and after 30, 60, 90 and 120 min from a 75 g glucose ingestion. Plasma AEA, related N-acylethanolamines palmitoylthanolamide (PEA) and oleoylthanolamide (OEA), 2AG and 1AG were measured by LC–MS/MS. A whole body and specific region composition analysis was performed by dual-energy X-ray absorptiometry. Basal insulin and glucose levels were 9.4 ± 1.1 \mu\text{mol}/ml and 91.0 ± 5.4 mg/dl, and the calculated area under curve (AUC) were 9.777 ± 3.701 and 4.244 ± 1.450, 1.498 ± 0.465 and 0.588 ± 0.192 pmol/ml respectively. AEA, PEA and OEA significantly decreased along OGTT (P = 0.004, P = 0.001 and P = 0.003 respectively). At 60 min their level (Δt(S−t0)) reduced to 0.639 ± 0.340 (51.4%), 9.16 ± 3.69 (41.2%) and 2.276 ± 0.906 pmol/ml (44.9%). Conversely, 2AG and 1AG levels did not significantly change. AEA, PEA and OEA reduction (Δt(S−t0)) negatively correlated with glucose AUC (r = 0.895, P = 0.040; r = 0.929, P = 0.022; r = -0.948, P = 0.014 respectively) and positively with whole body (r = 0.882, P = 0.048; r = 0.910, P = 0.032; r = 0.944, P = 0.016 respectively) and gynoid lean mass (r = 0.957, P = 0.010; r = 0.967, P = 0.007; r = 0.951, P = 0.013 respectively). No significant correlations were observed for BMI, waist circumference, basal glucose and insulin, adiponectin AUC and blood lipids. Our preliminary data indicated that N-acylethanolamines levels are suppressed during the OGTT, and that the extent of the suppression is promoted by lean mass and affected by increasing glucose AUC.

DOI: 10.1530/endoabs.32.P756

P757
Adiponectin and leptin actions on DNA synthesis and cell death of porcine myoblasts are dependent on the cellular milieu and related to ERK1/2 signalling
Judith Kuzinski\textsuperscript{1}, Katja Wili\textsuperscript{1}, Claudia Kalhe\textsuperscript{1}, Steffen Maak\textsuperscript{1}, Marie-France Palini\textsuperscript{1} & Charlotte Rechfeld\textsuperscript{1}
\textsuperscript{1}Leibniz Institute for Farm Animal Biology, Institute of Muscle Biology and Growth, Dummerstorf, Germany; \textsuperscript{2}Dairy and Swine R & D Centre, Agriculture and Agri-Food Canada, Sherbrooke, Canada.

Cross-talk between adipose tissue and skeletal muscle could be mediated in part by adipokines secreted from adipose tissue. Previously, we observed that adiponectin but not leptin decreased DNA synthesis rate in proliferating porcine myoblasts in growth factor-supplemented serum-free medium (GF-SFM) after 48-h exposure (Wili et al. 2012). To further elucidate the effects of adiponectin and leptin on muscle cell growth and their mode of action, this study was conducted to investigate the effects of these adipokines on cell number (DNA), DNA synthesis rate, and cell death as well as on the activation of key signalling molecules in proliferating porcine myoblasts either grown in low-serum (1% FBS) medium (LSM) or GF-SFM.

Recombinant porcine adiponectin (40 \mu\text{g}/ml) and leptin (20 \text{ng}/ml) supplemented to LSM increased DNA synthesis rate measured as (\textsuperscript{3}H)-thymidine incorporation (P < 0.01), probably related to increased DNA repair, and reduced cell viability in terms of lactate dehydrogenase release (P < 0.05) and/or lowered DNA content after 24-h (P < 0.05) but not 48-h exposure. Both adiponectin (P = 0.07) and leptin (P < 0.05) treatment resulted in an activation of ERK1/2 (p44-42) after 15 min followed by decreased activation after 60 and 180 min (P < 0.05). Adiponectin tended to increase c-fos activation (P = 0.08) and to decrease p53 activation at 180 min (P < 0.05). In GF-SFM, in contrast, adiponectin and leptin treatment decreased DNA synthesis as early as after 4-h exposure (P < 0.01) and diminished the rate of cell death after 48 h (P < 0.05). Under these conditions, ERK1/2 activation was reduced (P < 0.01) after 15- and 30-min treatment with adiponectin or leptin.

Conclusions, the effects of adiponectin and leptin on the growth of porcine myoblasts are dependent on the surrounding cellular milieu and related to ERK1/2 signalling. The presence of growth factors in culture medium seems to attenuate adverse effects of the adipokines on the growth of myoblasts.

Keywords Adiponectin, Leptin, Skeletal muscle, Pig, Satellite cell culture, ERK1/2.

DOI: 10.1530/endoabs.32.P757

P758
Body weight loss reverts obesity-associated hyponadotropic hypogonadism: a meta-analytic study
Giovanni Corona\textsuperscript{1}, Giulia Rastrelli\textsuperscript{2}, Matteo Monami\textsuperscript{3}, Farid Saad\textsuperscript{6}, Michaelu Lucioni\textsuperscript{1}, Marcello Lucchese\textsuperscript{7}, Alessandra Sforza\textsuperscript{8}, Gianni Forti\textsuperscript{9}, Edoardo Mannucci\textsuperscript{1} & Mario Maggi\textsuperscript{8}
\textsuperscript{1}Endocrinology Unit, Medico Chirurgico Department, Azienda Ul Bologna Maggiore-Bellaria Hospital, Bologna, Italy; \textsuperscript{2}Sexual Medicine and Andrology Unit, Department of Clinical Physiopathology, University of Florence, Florence, Italy; \textsuperscript{3}Diabetes Section Geriatric Unit, Department of Critical Care, University of Florence, Florence, Italy; \textsuperscript{4}Endocrinology Unit, Department of Clinical Physiopathology, University of Florence, Florence, Italy; \textsuperscript{5}Bariatric and Metabolic Surgery Unit, University of Florence, Florence, Florence, Italy; \textsuperscript{6}Bayer Schering Pharma AG, Berlin, Italy.

Introduction
Few randomised clinical studies have evaluated the impact of diet and physical activity on testosterone levels in obese men with conflicting results. Conversely, studies on bariatric surgery in men generally showed an increase in testosterone levels. The aim of the present study is to perform a systematic review and meta-analysis of available trials on the effect of body weight loss on sex hormones levels.

Methods
An extensive Medline search was performed including the following words 'testosterone', 'diet', 'weight loss' and 'bariatric surgery' and 'males'. The search was restricted to data from January 1, 1969 up to August 31, 2012.

Results
Out of 266 retrieved articles, 24 were included in the study. Of the latter, 22 evaluated the effect of diet or of bariatric surgery, whereas two compared diet and bariatric surgery. Overall both low calorie diet and bariatric surgery are associated with a significant (P < 0.0001) increase plasma sex hormone binding globulin bound and unbound testosterone levels (TT), bariatric surgery being more effective in comparison with low calorie diet (TT increase = 8.73 (6.51–10.95) vs 2.87 (1.68–4.07) for bariatric surgery and low calorie diet, respectively; both P < 0.0001 vs baseline). Androgen rise is greater in those patients that lose more weight as well as in younger, non-diabetic subjects with a greater degree of obesity. Body weight loss is also associated with and decrease in estradiol and increase in gonadotropins levels. Multiple regression analysis shows that the degree of body weight loss is the best determinant of TT rise (B = 2.50 ± 0.98; P = 0.029).

Conclusions
Present data show that weight loss is associated with an increase of both bound and unbound testosterone levels. The normalization of sex hormones induced by body weight loss is a possible mechanism contributing to the beneficial effects of surgery in morbid obesity.

DOI: 10.1530/endoabs.32.P758
P759

Serum levels of fetuin A and 8-hydroxydeoxyguanosine in morbidly obese subjects
Yildiz Dinçer1, Solen Himmetoglu2, Serkan Teksoz3, Kang Kzen3, Tuba Yesim4, and Mustafa Taskin5
1Department of Biochemistry, Cerrahpaşa Medical Faculty, Istanbul University, Istanbul, Turkey; 2Cerrahpaşa Laboratories, Istanbul, Turkey; 3Department of General Surgery, Cerrahpaşa Medical Faculty, Istanbul University, Istanbul, Turkey; 4Haseki Education and Research Hospital, Istanbul, Turkey.

Insulin resistance is one of the feature of obesity. Fetuin A is inhibitor of insulin receptor which belongs the family of receptor tyrosine kinase. It has been observed that fetuin-null mice are resistant to diet-induced obesity and they exhibit increased insulin sensitivity. Increased production of reactive oxygen species is suggested to be associated with insulin resistance. Attacks of reactive oxygen species to DNA results in base oxidation. Among the oxidized bases, 8-hydroxydeoxyguanosine is predominant lesion with pro-mutagenic potential. In the present study; measurement of serum levels of fetuin A and 8-hydroxydeoxyguanosine in obese subjects (n=46) and healthy controls (n=22), and examination of the relations between these parameters and insulin resistance have been pursued. Blood samples were taken form morbidly obese subjects after a 12 h fasting. Serum levels of fetuin A and 8-hydroxydeoxyguanosine were measured by ELISA. Statistical analysis was performed by Mann–Whitney U test and correlations were examined by Spearman’s correlation coefficient. Serum levels of total cholesterol, HDL, LDL, VLDL, triglycerides, T₃, T₄, fasting glucose, C-peptide and %HbA1c in the obese group were found to be different from those in the control group. Serum level of fetuin A was found to be higher, 8-hydroxydeoxyguanosine level was found to be lower in the morbid obese group than those in the control group. Fetuin A was found to be positively correlated with HOMA-IR and negatively correlated with 8-hydroxydeoxyguanosine. No significant association was determined between body mass index and measured parameters. In conclusion, serum level of fetuin A is high in morbidly obese subjects and is negatively associated with 8-hydroxydeoxyguanosine level in peripheral circulation. Fetuin A may be a promising link between insulin resistance and obesity as well its comorbidities.

DOI: 10.1530/endoabs.32.P759

P760

Off-label GLP-1 agonist treatment in 43 non-diabetic patients: are weight loss and treatment tolerance equally promising outside of clinical trials?
Nina Sauer, Zaina Rohani, Clarissa Schulze zur Wiesch, Franziska Reining & Jens Abele
Department of Endocrinology and Diabetology, Hamburg, Germany.

Context
Recent data from controlled clinical trials have demonstrated that GLP-1 agonists are a well-tolerated therapy option for weight loss in obese patients without type 2 diabetes mellitus.

Objective
To investigate whether continuation of treatment, side-effects and effect on weight loss of GLP-1 agonists are equally promising in daily clinical practice settings in non-diabetics.

Methods
Obese, non-diabetic patients of our interdisciplinary obesity centre were treated off-label with GLP-1 agonists. Application was started low dose and increased if therapy was common. Therefore long-term effect on weight-loss might not be as promising as suggested by data from clinical trials.

Conclusion
GLP 1 agonist treatment in obese non-diabetics also correlate with significant weight loss in clinical practice. However side-effects and discontinuation of treatment are common. There long-term effect on weight-loss might not be as promising as suggested by data from clinical trials.

DOI: 10.1530/endoabs.32.P760

P761

SHBG and testosterone are associated with inflammation in obese men
Jelena Milin-Lazovic1,2, Snežana Polovina1, Mirjana Sumarac-Dumanovic1,2, Danica Stamenkovic-Pejić1, Đanka Jeremić1, Goran Cvijovic1,2, Svjetlana Zorić1, Aleksandra Kendereski1,2 & Dragan Micic1,2
1Center for Obesity, Clinic for Endocrinology, Diabetes and Diseases of Metabolism, Belgrade, Serbia; 2School of Medicine, University of Belgrade, Belgrade, Serbia.

Introduction
It was showed that low SHBG represent an independent bio-marker of proinflammatory states associated with insulin resistance. Recent studies provide additional evidence that insulin plays no role in decreasing hepatic SHBG production, and that proinflammatory cytokines, contribute indirectly to reducing SHBG expression in obese men by reducing hepatic HNF-4α. Obesity in men is commonly accompanied by a decline of serum total testosterone and bioavailable testosterone (BT) levels. Metabolic syndrome (MetS) is associated with a further decline in testosterone, independently of BMI and SHBG, with dose-response relationship between decreasing levels of testosterone. Previous reports suggested hypothesis that androgens may have an anti-inflammatory effect. The aim of the study was to examine the association between testosterone and SHBG to C-reactive protein (CRP) and insulin resistance in obese men.

Description of methods/design
We investigated 52 obese men mean age: 38.91 ±12.56 years; mean BMI: 46.11 ±10.37 kg/m²) and measured SHBG, testosterone, CRP, fasting plasma glucose, fasting plasma insulin, HOMA-IR and anthropometric measurements (BMI, WC, WHR).

Results
SHBG was significantly inversely correlated with CRP (r = -0.615, P<0.001) and fasting insulin (r = -0.291, P<0.05). There was no statistically significant correlation between SHBG and fasting plasma glucose, HOMA-IR and BMI< WC, WHR. Levels of testosterone were inversely correlated with CRP (r = -0.341, P<0.005), BMI (r = -0.461, P<0.001) and WC (r = -0.389, P<0.001). There was no statistically significant correlation between testosterone and fasting insulin, fasting glucose, HOMA-IR or WHR.

Conclusion
Our result suggested association of low levels of testosterone and SHBG with increased inflammation in obese man.

DOI: 10.1530/endoabs.32.P761

P762

The effect of rutin on homocysteine induced proliferation of 3T3-L1 preadipocyte in vitro
Sung Hoon Yu1, Jun Goo Kang1, Yoe-Choel Hwang2, Hong Yup Ahn3, Cheol-Young Park4, Dong Sun Kim5 & Hyung Joon Yoo1
1Division of Endocrinology and Metabolism, Department of Internal Medicine, Hallym University College of Medicine, Seoul, Republic of Korea; 2Division of Endocrinology and Metabolism, Department of Medicine, Kyung Hee University Hospital at Gangdong, Kyung Hee University School of Medicine, Seoul, Republic of Korea; 3Department of Statistics, Dongguk University-Seoul, Seoul, Republic of Korea; 4Division of Endocrinology and Metabolism, Department of Internal Medicine, School of Medicine Sungkyunkwan University, Seoul, Republic of Korea; 5Division of Endocrinology and Metabolism, Department of Internal Medicine, Hanyang University College of Medicine, Seoul, Republic of Korea.

Introduction
Rutin (C₂₃H₂₆O₁₄a) is the major representative of the flavonol subclass of flavonoids. Rutin has wide variety of pharmacological activity, however there are not sufficient data in 3T3-L1 preadipocyte. In this study, we demonstrated that the effect of rutin on the proliferation of 3T3-L1 preadipocyte.

Methods
The 3T3-L1 preadipocyte were treated with homocysteine (1 mM), rutin (30 μM) and rutin after homocysteine. And we analyzed the cell proliferation with 3T3-L1 preadipocyte. We investigated 52 obese men mean age: 38.91 ±12.56 years; mean BMI: 46.11 ±10.37 kg/m²) and measured SHBG, testosterone, CRP, fasting plasma glucose, fasting plasma testosterone, HOMA-IR and anthropometric measurements (BMI, WC, WHR).

Results
SHBG was significantly inversely correlated with CRP (r = -0.615, P<0.001) and fasting insulin (r = -0.291, P<0.05). There was no statistically significant correlation between SHBG and fasting plasma glucose, HOMA-IR and BMI< WC, WHR. Levels of testosterone were inversely correlated with CRP (r = -0.341, P<0.005), BMI (r = -0.461, P<0.001) and WC (r = -0.389, P<0.001). There was no statistically significant correlation between testosterone and fasting insulin, fasting glucose, HOMA-IR or WHR.

Conclusion
Our result suggested association of low levels of testosterone and SHBG with increased inflammation in obese man.

DOI: 10.1530/endoabs.32.P761

Endocrine Abstracts (2013) Vol 32
methylthiazolyltetrazolium (MTT) assay. We evaluated the proliferation pathway with Western blot.

Results

The proliferation of 3T3-L1 preadipocyte was enhanced with homocysteine (P < 0.001). The cell viability of 3T3-L1 preadipocyte was not changed with rutin in diverse doses (5, 10, 30, 60 μM). But rutin after homocysteine treatment significantly suppressed the proliferation of 3T3-L1 preadipocyte compared to homocysteine treatment. In Western blot analysis, Immunoreexpression of phosphorylated p44/42 MAPK (ERK1/2) and phospho-MEK1/2 were significantly increased by homocysteine (1 mM). However, these were suppressed with PD98059 treatment, not by wortmannin treatment.

Conclusion

These results suggested rutin suppressed the proliferation of 3T3-L1 preadipocyte by homocysteine through p44/42 MAPK pathway.

DOI: 10.1530/endoabs.32.P762

P763

Preoperative metabolic status is associated with adiponectin levels attained 6 months after laparoscopic sleeve gastrectomy, independently of the degree of weight loss.

A. Sirbu1,2, S. Martinî1,2, C. Barbu1,2, C. Copacescu3, S. Florea3 & S. Fica1,2

1Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; 2Elias University Hospital, Bucharest, Romania; 3Delta Hospital, Bucharest, Romania.

Introduction

Adiponectin is an adipocyte-derived hormone with an important role in regulation of glucose and lipid metabolism. Its variation might mediate an ameliorated metabolic profile associated with weight loss after bariatric surgery. The aim of our study was to evaluate adiponectin change as early as 6 months after laparoscopic sleeve gastrectomy (LSG) and to indicate preoperative factors that might influence its dynamic.

Methods

A number of 88 extremely obese women (mean age = 42.1 ± 11.24 years, mean BMI = 45.77 ± 7.6 kg/m²) were evaluated before and after 6 months from LSG. This included complete clinical examination, as well as metabolic and hormonal lab tests. Serum adiponectin was measured using ELISA method, while for C-reactive protein (CRP), IGFl and insulin we used chemiluminescence. Since IGFl levels are age-dependent, we calculated the SDS of IGFl levels according to age (z-score). Parametric variables are presented as mean ± s.d., while non-parametric ones (such as adiponectin) as median (interquartile range).

Results

Six months after LSG, mean BMI decreased from 45.77 ± 7.6 to 33.24 ± 7.1 kg/m², P < 0.001, while adiponectin levels increased from 7.76 (3.74) to 10.4 (6.57) mg/l, P < 0.001. Postoperative adiponectin levels negatively correlated with preoperative triglyceride (r = −0.294, P = 0.008), HOMA-IR (r = −0.326, P = 0.005), and CRP (r = −0.337, P = 0.004) levels and positively correlated with preoperative adiponectin levels (r = 0.442, P < 0.001) and IGFl z-score (r = 0.245, P = 0.029). There was also a positive correlation between postoperative adiponectin levels and the percentage of weight loss (r = 0.318, P = 0.004). In multivariate analysis, stepwise method, which included all the aforementioned variables, preoperative adiponectin and HOMA-IR levels and the percentage of weight loss remained independently associated with postoperative adiponectin levels, together explaining 52.7% of its variability.

Conclusion

Preoperative metabolic status (appreciated by adiponectin and HOMA-IR levels) and the percentage of weight loss are independent determinants of adiponectin levels attained 6 months after LSG.

DOI: 10.1530/endoabs.32.P763

P765

Evaluation of the prevalence of obesity and overweight in the Belarus within the Framework of the National Campaign ‘Early Detection and Prevention of Type 2 Diabetes Mellitus’

A. Shapelkevich1, O. Balbo1, H. Holodova1, V. Lobashova1, I. Bilodid1, L. Pedchenets1, L. Kovshik1, M. Tulupova1, A. Grigorovich2, O. Zalesskaya3 & V. Selivanov1

1Belarussian State Medical University, Minsk, Belarus; 2State Institution ‘Republican Centre for Medical Rehabilitation and Balneotherapy, Minsk, Belarus; 3Healthcare Institution ‘City Endocrinological Dispensary of Minsk, Minsk, Belarus.’

Objective

To evaluate the gastric bypass effect in type 2 diabetic patients with morbid obesity, on the following terms: diabetes evolution, 10 years estimated cardiovascular risk and quality of life

Methods

Cohort study with intrasubject measures (before-after) in a sample of patients with morbid obesity and type 2 diabetes who underwent gastric bypass. Demographic characteristics, anthropometric parameters, cardiovascular risk factors and surgical complications were analyzed. The estimation of cardiovascular disease risk at 10 years was determined according to the Framingham Risk Score and the impact on the quality of life using the BAROS test (Bariatric Analysis and Reporting Outcome System).

Results

41 patients were included (63.4% female), with mean age 45.62 ± 8.37 years and BMI before surgery 51.96 ± 8.69 kg/m². In most cases duration of diabetes was < 10 years, 92.6% used oral hypoglycemic therapy and with not known chronic complications. Mean HbA1c before surgery was 7.55 ± 1.18 and 5.33 ± 0.59% at 2 years. Four months after the bypass only 12 patients maintained the diagnosis of diabetes. Two years after surgery the percentage of weight lost was 65.81% and the resolution of hypertension, dyslipidemia and diabetes occurred in 76.67, 89.29, and 92.68% cases respectively (P < 0.001). According to the Framingham Risk Score, estimated 10 years cardiovascular risk was greater than 20% in 35.9% of cases before surgery. Mean risk decreased from 15.84% at baseline to 4.32% two years after surgery (P < 0.001). 14.6% of patients had early complications and 19.5% developed later complications. BAROS scale was excellent in 36.8% of cases, very good in 36.7% and good in 21.1% at 2 years.

Conclusions

In morbid obese patients with type 2 diabetes, gastric bypass was shown as an effective tool in the early resolution of diabetes, besides its beneficial effects on 10 years estimated cardiovascular risk and quality of life.

DOI: 10.1530/endoabs.32.P764

P764

Evaluation of gastric bypass effect on cardiovascular risk and quality of life in type 2 diabetes patients


Endocrinology Department, University Hospital Puerta del Mar, Cádiz, Spain.

Objective

To evaluate the gastric bypass effect in type 2 diabetic patients with morbid obesity, on the following terms: diabetes evolution, 10 years estimated cardiovascular risk and quality of life

Methods

Cohort study with intrasubject measures (before-after) in a sample of patients with morbid obesity and type 2 diabetes who underwent gastric bypass. Demographic characteristics, anthropometric parameters, cardiovascular risk factors and surgical complications were analyzed. The estimation of cardiovascular disease risk at 10 years was determined according to the Framingham Risk Score and the impact on the quality of life using the BAROS test (Bariatric Analysis and Reporting Outcome System).

Results

41 patients were included (63.4% female), with mean age 45.62 ± 8.37 years and BMI before surgery 51.96 ± 8.69 kg/m². In most cases duration of diabetes was < 10 years, 92.6% used oral hypoglycemic therapy and with not known chronic complications. Mean HbA1c before surgery was 7.55 ± 1.18 and 5.33 ± 0.59% at 2 years. Four months after the bypass only 12 patients maintained the diagnosis of diabetes. Two years after surgery the percentage of weight lost was 65.81% and the resolution of hypertension, dyslipidemia and diabetes occurred in 76.67, 89.29, and 92.68% cases respectively (P < 0.001). According to the Framingham Risk Score, estimated 10 years cardiovascular risk was greater than 20% in 35.9% of cases before surgery. Mean risk decreased from 15.84% at baseline to 4.32% two years after surgery (P < 0.001). 14.6% of patients had early complications and 19.5% developed later complications. BAROS scale was excellent in 36.8% of cases, very good in 36.7% and good in 21.1% at 2 years.

Conclusions

In morbid obese patients with type 2 diabetes, gastric bypass was shown as an effective tool in the early resolution of diabetes, besides its beneficial effects on 10 years estimated cardiovascular risk and quality of life.

DOI: 10.1530/endoabs.32.P764

Endocrine Abstracts (2013) Vol 32
developing type 2 diabetes was registered in 934 (20.29%) males and in 3551 (32.66%) females.

Conclusions
The results of the National Campaign ‘Early Detection and Prevention of Type 2 Diabetes Mellitus’ testify to the presence of high percent of overweight (44.09%) and obesity (26.17%) in Belarusian population.

DOI: 10.1530/endoabs.32.P765

P766
No long-term weight reduction after gastric banding (LAGB) in obese patients with craniopharyngioma involving hypothalamic structures: experiences from KRANIOPHARYNGEOM 2000
Anthe Sterkenburg1,2, Ursel Gebhardt1, Anika Hoffmann1, Jörn Maroske1, Ernst Hanisch1 & Hermann Müller1
1Department of Pediatrics, Klinikum Oldenburg, Oldenburg, Germany; 2University Hospital Groningen (UMCG), Groningen, The Netherlands;
3Department of Surgery, Verbundklinikum Rothenburg o.d.Tauern, Rothenburg, Germany; 4Department of General, Visceral, and Endocrine Surgery, Asklepios Klinik, Langen, Germany.

Background
Craniopharyngiomas are embryonic malformations which lead to eating disorders and morbid obesity due to hypothalamic involvement. The experience with laparoscopic adjustable gastric banding (LAGB) in obese craniopharyngioma patients is limited especially in regard to long-term effects and tolerability.

Patients and methods:
We are reporting on four patients with childhood craniopharyngioma diagnosed at age 2, 13, 12, and 20 years.

Results
BMI–SDS at diagnosis was −0.9, +4.5, +4.7 and +0.23 s.d. All patients developed morbid obesity (BMI–SDS: +10.87, +10.36, +11.4, +6.2) so that 11, 5, 9 and 3 years after diagnosis LAGB were performed. LAGB were well tolerated. During long-term follow-up, the nadir BMI–SDS (+6.9, +9.5, +7.8, +4.9) were reached 2.0, 0.3, 1.0, 0.8 years after LAGB. At last evaluation 9.1, 5.3, 7.1, 7.1 years after LAGB, the patients BMI (BMI–SDS at last evaluation: +10.2, +13.9, +10.2, +6.3) had increased again but remained at a constant level comparable with baseline BMI–SDS at the time of LAGB. Quality of life was not decreased due to LAGB and tolerability was sufficient.

Conclusions
We conclude that LAGB is feasible and could have clinical relevant effects on long-term weight stabilization of obese craniopharyngioma patients with hypothalamic syndrome. However, a significant weight reduction was not achieved after LAGB in patients with childhood craniopharyngioma. Non-reversible bariatric procedures such as gastric bypass are not recommended for treatment of obese children and adolescents with craniopharyngioma due to ethical considerations.

DOI: 10.1530/endoabs.32.P766

P767
Long-term weight development and psychosocial status in childhood craniopharyngioma patients
Anthe Sterkenburg1,2, Anika Hoffmann1, Ursel Gebhardt1 & Hermann Müller1
1Department of Pediatrics, Klinikum Oldenburg, Oldenburg, Germany; 2University Hospital Groningen (UMCG), Groningen, The Netherlands.

Background
Craniopharyngioma (CP) are the most common sellar tumors in children. Patients often develop excessive weight gain and obesity due to several factors as involvement or damage of the hypothalamus. Previous studies on the weight development in craniopharyngioma patients have shown an increase in weight before and after the first 10 years after diagnosis leading to an impaired quality of life. The long-term weight development in these patients has not been investigated till now.

Methods
In a retrospective study, we analysed the weight development of 108 craniopharyngioma patients who were diagnosed before 2001. Data from physical examinations, anthropometric measurements and the patient’s records were used, as well as a questionnaire answered by the patients in 2011 on their current weight and psychosocial status. The BMI of CP patients at diagnosis, 8–12 years after diagnosis, during long-term follow-up and at the time they answered the questionnaire was analysed and factors were investigated for their effect on the weight development.

Conclusions
Long-term survivors of CP were assessed at a median age of 26.1 years (range 14.8–42.7) after a median follow-up of 17.01 years (range 8.81–33.40) after CP diagnosis. All patients show an increase in BMI during the first 10 years after diagnosis, as previously published. However, during long-term follow-up (more than 12 years after diagnosis) no further weight increase is seen. Patients with hypothalamic involvement of CP develop a higher initial weight increase, but also a stabilisation of BMI as well. Patients with a normal BMI at diagnosis (−2 to +2 s.d.) show the highest weight increase during the first 10 years after diagnosis, whereas patients presenting with obesity at diagnosis (BMI > 3 s.d.) show a smaller increase in BMI–SDS during long-term follow-up.

We conclude that the degree of obesity in CP reaches a certain plateau during long-term follow-up.

DOI: 10.1530/endoabs.32.P767

P768
Assessment of dietary habits in obese patients
Inmaculada González-Molero, Marta Domínguez-López, MArisol Ruiz de Adana & Federico Soriguer
Endocrinology Service, Carlos Haya Hospital, Málaga, Spain.

Introduction
A key factor in the progressive increase in the prevalence of obesity is poor dietary habits. The treatment of obesity with regular diets often fail, so knowing the specific habits of these patients can be very useful to individualize treatment.

Objective
Evaluate the dietary habits of subjects consulting for obesity in our clinic of Endocrinology and Nutrition

Materials and methods
We conducted a survey of eating habits for overweight and obese patients (Brown et al., Castro et al.) in all patients who consulted for this reason during previous 2 months. We collected data on age, sex, cardiovascular risk factors, anthropometric (weight, height, BMI, waist circumference) and laboratory parameters.

Results
Data from 68 patients were collected. The mean age was 52.8±17.5 years, 34.4% males. 64.7% had diabetes, with a mean HbA1c of 7.52%, 30% were hypertensive and 58.8% dyslipidemic. Mean BMI at first visit was 39.77±5.45 and BMI at the time of the survey was 37.62±7.24 (66.7% between 25 and 40% and 33.5% over 40%). Mean weight: 112.0±24.36 kg initially vs 105.1±21.77 kg finally, with a mean follow-up of 2.9±2.1 years. 81.3% had received dietary advice by a dietitian. 28.5% of patients responded correctly to more than 75% of questions, 35.3% between 50 and 75% and 32.1% responded adequately to <50%. Subjectively, patients thought their diet was poor, fair, good, very good and excellent in 3.6, 53.6, 32.1, 10.7 and 0% respectively. There was a significant association between subjective scores and dietary questionnaire, so that subjects who responded appropriately to more than 75% felt that their diet was poor, fair, good or very good in 0, 25, 50 and 25% of cases and subjects who responded correctly to <50% of questionnaire felt that their diet was poor in 11.1%, fair in 77.8% and good in 11.1% (P = 0.007).

Presence of adequate habits (over 75% correctly responses) was significantly associated with instruction by the dietitian (34.8% in instructed vs 0% in subjects not instructed. P = 0.047) but there was no association to any other features studied: BMI (22.2% in morbid vs 23.5% in no morbid obese), sex (35.3% in women vs 18.2% in men), age (31.6% in >40 years vs 22.2% in <40 years), diabetes (25% in diabetics vs 33.3% in non-diabetics), hypertension (35.7% in 21.4%) or dyslipidemia (28.6% vs 28.6%)

Conclusions
Although dietary education improves eating habits of obese patients, a high percentage remain with inadequate dietetic costumes, which could be a key factor in the failure of obesity treatment.

DOI: 10.1530/endoabs.32.P768

P769
Sub clinical hypercortisism in patients with metabolic syndrome
Mona Mansour1,2, Randa Abdou1 & Fatma El Mogy1,2
1Endocrinology Department, Cairo university, Cairo, Egypt; 2Pathology Department, Cairo university, Cairo, Egypt.

Objectives
Patients with metabolic syndrome who presents with vascular, metabolic or bone disorders of recent onset, or are difficult to control, or are progressively
deteriorating is potentially linked to cortisol excess the aim of the study is to evaluate the prevalence of occult CS in metabolic syndrome patients. 

Method 
In a cross-sectional study, 30 females with metabolic syndrome chosen from Endocrinology Clinic without any pathological features of Cushing’s syndrome were subjected to: full history taking, clinical evaluation, BMI, waist circumference, fasting and pp blood sugar, lipid profile and overnight 1 mg dexamethasone suppression test (DST).

Results
Among the 30 patients in the study, three patients (10%) didn’t show positive dexamethasone suppression test (occult Cushing’s syndrome) and the rest of the patients (27) showed positive test.

Conclusion
A relatively high prevalence of occult CS was found in our study. Further studies are needed to provide a rationale for systematic screening of occult CS in this population. To be of benefit by reducing the period of time spent in the atherosclerotic, catabolic, and thrombotic milieu of hypercortisolism.

Keywords
sub-clinical, Cushing’s, diabetes, metabolic syndrome.

DOI: 10.1530/endoabs.32.P769

P770
Testosterone concentrations in obesity, an outcome of lipotoxicity? 

Marlies Bekaert1, Yves Van Nieuenwoude2, Patrick Calder3, Jean-Marc Kaufman1, Margriet Ouwens4,1 & Johannes Ruige1

1Endocrinology, University Hospital Ghent, Ghent, Belgium; 2Abdominal Surgery, University Hospital Ghent, Ghent, Belgium; 3Revalidation Science and Physiotherapy, University Hospital Ghent, Ghent, Belgium; 4Institute for Clinical Biochemistry and Pathobiochemistry, German Diabetes Center, Düsseldorf, Germany.

Objective
Testosterone levels are decreased in male obesity, the mechanism of which is incompletely understood. The aim of this study was to explore determinants affecting the feedback mechanism of the hypothalamic–pituitary–gonadal axis in incompletely understood. The aim of this study was to explore determinants affecting the feedback mechanism of the hypothalamic–pituitary–gonadal axis in

Materials and methods
Circulating levels of testosterone were quantified (<1000 ng/l with LC–MS/MS) in 37 middle-aged morbidly obese men (of which 23 had DM2) and 19 non-obese controls of similar age. LH and triglyceride levels were measured through standardized assays and aromatase expression was determined in subcutaneous adipose tissue biopsies using real-time PCR analysis.

Results
Mean testosterone levels were different among the groups, with 572, 372 and 207 ng/dl in non-obese, morbidly obese and morbidly obese men with DM2 respectively (P<0.001). Statistical differences in LH levels could not be established. Median triglyceride levels were higher in obese men vs non-obese men (P<0.05), with 96, 154 and 148 mg/dl in non-obese, morbidly obese and morbidly obese men with DM2 respectively. In non-obese men, age-adjusted Pearson’s analysis showed that testosterone levels correlated positively with LH (r=0.490, P=0.054) and inversely with aromatase expression (r = -0.635, P=0.036). In obese men, an inverse association was found between testosterone and triglyceride levels (r = -0.715, P=0.013). Although in obese men with DM2 correlations with testosterone could not be established, LH was inversely correlated with triglyceride concentrations (r = -0.535, P=0.010).

Conclusion
Although testosterone in normal men may depend on aromatase activity, these data show that testosterone concentrations in male obesity are inversely associated with triglyceride concentrations, which have been suggested as a marker of lipotoxicity.

DOI: 10.1530/endoabs.32.P770

P771
Hyponogadal men receiving testosterone treatment for 5 years had significant and clinically meaningful reductions in weight and waist circumference

Farid Saad1,2, Aksam Yassin3,4, Gheorghe Doros5 & Abdulmaged Train6

1Bayer Pharma AG, Berlin, Germany; 2Gulf Medical University School of Medicine, Ajman, United Arab Emirates; 3Institute for Urology and Andrology, Norderstedt, Germany; 4Dresden International University, Dresden, Germany; 5Boston University School of Public Health, Boston, Massachusetts, USA; 6Boston University School of Medicine, Boston, Massachusetts, USA.

Objective
This study investigated effects of testosterone replacement therapy (TRT) on the metabolic syndrome in hyponogadal men over 5 years.

Methods
Cumulative, prospective registry study of 164 men with erectile dysfunction and testosterone below 12 nmol/l presenting to a urological institution. All patients received testosterone undecanoate injections 1000 mg every 12 weeks following an initial 6-week interval for a total of 5 years.

Results
After 5 years, mean weight decreased from 104.35±13.84 (minimum 74.0, maximum 141.00) to 92.49±11.15 (minimum 67.0; maximum 124.0). This decrease was statistically significant vs baseline (P<0.0001) and each year compared to the previous year. Mean change of baseline was −9.79±0.35%. After 5 years, 96% of men had lost any weight, 8% had lost ≥5%, 58% ≥10%, 34% ≥15%, and 18% ≥20%.

Waist circumference (cm) decreased from 108.61±10.13 (minimum 88.00; maximum 148.00) to 99.63±9.05 (minimum 85.00; maximum 137.00); 98% had any reduction in waist size. 84% ≥5, 48% ≥10, 15% ≥15 cm. BMI declined from 33.21±4.23 (minimum 24.96; maximum 43.10) to 29.42±3.37 (minimum 19.58; maximum 37.39) (P<0.0001 vs baseline for all values).

Fasting glucose decreased from 112.77±55.87 to 99.02±18.1 mg/dl. HbA1c from 6.73±1.27 to 5.63±0.64. Total cholesterol declined from 264.24±49.16 to 212.2±40.88 mg/dl. LDL from 162.31±26.28 to 126.41±33.7 mg/dl. triglycerides from 261.07±89.16 to 199.04±52.34 mg/dl. HDL increased from 40.15±13.04 to 55.62±14.66 mg/dl. Systolic blood pressure decreased from 140.01±13.61 to 122.35±5.96 mmHg, diastolic from 81.67±9.55 to 77.68±4.07 mmHg (P<0.0001 for all).

Conclusions
TRT resulted in improvements of all components of the metabolic syndrome. Reductions of weight and waist circumference were progressive and statistically significant over the full 5 years of the study.

DOI: 10.1530/endoabs.32.P771

P772
Moderating role of cognitive ability on the obesity: inflammation: insulin resistance triplet

Eirini Spyridaki, Andrew Margiornis, Panagiotsis Simos, Pavlina Avgoustinaki & Eirini Dermitzaki

School of Medicine, University of Crete, Heraklion, Crete, Greece.

Obesity, the condition resulting from excess of body fat, is often accompanied by chronic low-grade levels of inflammation. These have been strongly associated with the development of insulin resistance (IR). Elevated BMI has also been linked to reduced cognitive performance, especially in executive functions, independently of medical co-morbidities.

Aim of this research is to investigate whether higher cognitive resources may present a moderating, ‘protective’ role on the triplet obesity – inflammation – insulin resistance.

Community-dwelling adults (n=127, M age=37.35, s.d. =14.17, range 17–65 years; 85% females) free of major and chronic autoimmune or inflammatory diseases underwent blood test after overnight fasting. C-reactive protein (CRP), a major marker of systemic inflammation, and Homeostatic Model Assessment, a widely used method to yield IR from fasting plasma insulin and glucose concentrations, were measured. Cognitive resources were evaluated through the General Adult Mental Ability Scale (GAMA), a non-verbal measure of general intelligence.

Moderated mediation analyses were performed comparing two alternative models. In model 1 a conditional indirect effect of BMI (obesity) on HOMA (insulin resistance), which is mediated by CRP (inflammation) was tested. Our interim results showed that the strength of the association between BMI and CRP varied at different levels of cognitive ability: the effect of obesity on inflammation was stronger for persons with poorer cognitive ability (controlling for age and education level). In a second proposed model, a direct effect of CRP (inflammation) on HOMA (insulin resistance), moderated by GAMA (cognitive ability) was tested. BMI was found to exert a direct effect on HOMA but the association between CRP and HOMA was not affected by cognitive ability.

DOI: 10.1530/endoabs.32.P772
P773
Should all the obese patients be screened for Cushing’s syndrome?
Serap Baydar Sahin1, Hacer Sezgin2, Kadir Ilkcik3, Emine Uluo Gur1 & Teslim Ayaz1

1Department of Endocrinology and Metabolism Disease, Recep Tayyip Erdogan University Medical School, Rize, Turkey; 2Department of Family Medicine, Recep Tayyip Erdogan University Medical School, Rize, Turkey; 3Department of Internal Medicine, Recep Tayyip Erdogan University Medical School, Rize, Turkey.

Background
Cushing’s syndrome (CS) is a relatively unusual condition that resembles many of the phenotypic features of obesity. The 1-mg dexamethasone suppression test (1 mg-DST) is the most frequently used screening tool for CS. However, the lack of suppression after 1 mg-DST may be found in obese patients. In the current study, our aim was to evaluate the clinical signs of CS and the 1 mg-DST in obese patients.

Materials and methods
354 patients (87.9% females, age 37.8 ±13.4 years) who admitted to our outpatient clinic for obesity enrolled in this study. All the patients were evaluated for the clinical signs of CS. Weight, BMI, waist circumference, blood pressure were recorded. None of the patients used pharmacological glucocorticoid therapy.

Lipid parameters, fasting glucose (FPG) and insulin, 75 g OGTT, basal cortisol and ACTH were measured. 1 mg-DST was performed.

Results
The mean FPG, insulin levels and HOMA-IR were 112.49 G 36.2% of the patients had central obesity, 72% dorsocervical fat accumulation, 12.01 G 2.03 respectively. The mean cortisol and ACTH levels were as follows: 9.28 G 3.53 g/dl and 17.02 ±10.43 pg/ml. Seven patients failed to suppress plasma cortisol to <1.8 g/dl. Biochemical confirmation tests were performed in these patients and two of them were diagnosed glucocorticoid-secreting adrenal adenoma.

Conclusions
As a result of our study, 0.5% of the obese patients were diagnosed Cushing’s syndrome and 1.4% of the patients had false-positive 1 mg-DST.

DOI: 10.1530/endobsds.32.P773

P774
Diabetes remission after bariatric surgery may be jeopardized by remission criteria and previous hypoglycemic treatment
Ana Ramos-Levi1, Andres Sanchez-Pernaute2, Carmen Hernandez2, Alfonso Calle-Pascual1, Antonio Torres1 & Miguel Rubio1

1Department of Endocrinology and Nutrition, IDISSC, Hospital Clinico San Carlos, Madrid, Spain; 2Department of Surgery, IDISSC, Hospital Clinico San Carlos, Madrid, Spain.

Introduction
Diabetes remission after bariatric surgery may be jeopardized by remission criteria and previous hypoglycemic treatment. Attention to individuals who do not strictly fulfill remission criteria has been frequently left behind. The aim of this study was to evaluate metabolic control status in patients considered as diabetes ‘non-remitters’.

Materials and methods
Retrospective study of 125 patients (59.2% women) with preoperative diagnosis of T2D who underwent BS in a single centre (2006–2011). Anthropometric and metabolic parameters, before surgery and at one-year follow-up. Definition of T2D remission according to Buse et al.: HbA1c <6%, fasting glucose (FG) <100 mg/dl, absence of pharmacologic treatment. Analysis of non-remitters and their metabolic status according to ADA’s target recommendations of glucose and lipid control: HbA1c <7%, c-LDL <100 mg/dl, triglycerides <150 mg/d, chDL >40 (male) or >50 mg/dl (female). Statistics: ANOVA.

Results
Preoperatively (mean ± s.d.): age 53.5 ± 9.7 years, BMI 43.5 ± 5.6 kg/m2, duration of T2D 7.7 ± 7.9 years, FG 162.0 ± 56.3 mg/dl, HbA1c 7.7 ± 1.6%. At baseline, ADA’s target recommendations were present in 12 (9.6%) and at one year follow-up in 45 (36%) individuals (P <0.000). 62 (49.6%) patients did not achieve diabetes remission; 26 (41.9%) had now diet treatment only, 30 (48.4%) oral medications and 6 (9.7%) required insulin. Of the non-remitters, 57 (91.9%) had HbA1c <7 and 18 (40.0%) achieved ADA’s target recommendations. There were no differences between remitters and non-remitters in the number of individuals reaching ADA’s target glucose and lipid levels.

Conclusions
Although almost 50% of patients may not be classified as diabetes remitters, they achieve a significant improvement in glucose and lipid control, which should be considered a success according to most scientific societies’ target recommendations.

DOI: 10.1530/endobsds.32.P775

P775
Should remission of type 2 diabetes mellitus be the foremost goal after bariatric surgery?
Ana Ramos-Levi1, Pilar Matia1, Lucia Cabreroz1, Ana Barabash1, Andres Sanchez-Pernaute2, Carmen Hernandez2, Alfonso Calle-Pascual1, Antonio Torres1 & Miguel Rubio1

1Department of Endocrinology and Nutrition, IDISSC, Hospital Clinico San Carlos, Madrid, Spain; 2Department of Surgery, IDISSC, Hospital Clinico San Carlos, Madrid, Spain.

Introduction
Remission of type 2 diabetes (T2D) is a yearned outcome after bariatric surgery (BS). Prior insulin use is a main setback for remission. Longer diabetes duration, lower %WL, %EWL and baseline C-peptide, higher age and female sex were associated to non-remission.

Conclusions
Base criteria reveal lower T2D remission rates after BS than previously reported. Prior insulin use is a main setback for remission. Longer diabetes duration, lower %WL, %EWL and baseline C-peptide, higher age and female sex were associated to non-remission.

DOI: 10.1530/endobsds.32.P774

P776
Development of metabolic syndrome is influenced by the thyroid function and age
Tatiana Mityukova1, Natalia Akulevich1, Maxim Lushchyk1, Tatiana Leonavova2, Tamara Platonoval3 & Valentina Drozdov1

1Belarusian Medical Academy of Post-Graduate Education, Minsk, Belarus; 2International Fund ‘Arnika’, Minsk, Belarus.

A lot of new data have been recently generated regarding the complex relationship between the thyroid function and metabolic parameters. The aim of the study was to estimate the obesity and metabolic syndrome (MS) rates according to the age and the thyroid function in the residents of Belarus.

We have examined 894 subjects aged 18–44 years (82.2% females) living in Stolin district, Brest region of Belarus. The endocrinological examination with anthropometric measurements, the thyroid ultrasound, thyroid function tests and blood biochemistry were performed. The central obesity was diagnosed according to the IDF criteria.

Waist circumference exceeded the IDF cut-off levels in 68.1% of the studied population (71.8% females and 50.9% males). The MS (central obesity +2 or more the IDF factors) was diagnosed in 29% of the whole population: only in 5% of subjects at the age of 18–19, in 19% of 20–29 years old, in 32% of aged 30–39

Endocrine Abstracts (2013) Vol 32
Pharmaceutical, Medical School Novi Sad University of Novi Sad, Novi Sad, Vojvodina, Serbia; 2Emergency Center, Clinical Center of Vojvodina, Novi Sad, Vojvodina, Serbia; 3Medical Center Ruma, Ruma, Vojvodina, Serbia; 4Institute of Laboratory Medicine, Clinical Center of Vojvodina, Novi Sad, Vojvodina, Serbia; 5Medical School, University of Novi Sad, Novi Sad, Vojvodina, Serbia.

Background

Phthalates present endocrine disruptors widely used as plasticisers, solvents and additives in many consumer products. Experimental data and human cross-sectional studies suggest association of phthalates and obesity. This study focused to association between urinary levels of some phthalate metabolites and BMI and waist circumference.

Methods

We recruited 87 obese persons (44 females and 43 males), age 38.57 ± 8.14 years and 103 healthy controls (52 females and 51 males) similar age. Waist circumference was measured and BMI was calculated. Phthalate monoester metabolites (mono(2-ethylhexyl)phthalate (MEHP), mono(butylphthalate (MBP), and mono(2-ethylhexyl) phthalate (MEHP)) were measured in single spot urine by mass spectrometry.

Results

BMI (35.28 ± 8.14 vs 22.85 ± 2.10 kg/m², P < 0.001) and waist circumference (110.85 ± 15.35 vs 78.38 ± 8.03 cm, P < 0.001) were significantly higher in obese than in controls. All urinary phthalate metabolites were higher in obese than in controls, but non significant (MEP 52.53 ± 141.89 vs 32.89 ± 128.99 MBP 21.52 ± 134.30 vs 10.25 ± 79.44 MEHP 20.83 ± 56.40 vs 19.90 ± 56.94 ng/mL). There are no any differences in levels urinary phthalate levels between genders in both groups. Only MBP had significant positive correlation with BMI (r=0.201; P<0.05) and waist circumference (r=0.198; P<0.05) in all participants who were positive for urinary phthalate metabolites.

Conclusion

The association between dibutylphthalate (DBP) and some parameters of obesity is possible. Further studies have to confirm and elucidate this association.

DOI: 10.1530/endoabs.32.P779

P779

‘Diabesity’ in women: the EEM study

Wilfredo Guanipa-Sierra1, Martha Sánchez-Zambrano2, Josefina Feijoo2, Rita Pizzi3 & Ingrid Márquez2

1Dr Alfredo Van Grieken University Hospital, Coro, Falcón, Venezuela; 2De Domingo Luciani Hospital, Caracas, Distrito Capital, Venezuela; 3Caracas University Hospital, Caracas, Distrito Capital, Venezuela.

‘Diabesity’ is the term for diabetes occurring in the context of obesity. Obesity is a cardiovascular major risk factor. The National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) report designated diabetes as a coronary heart disease equivalent. Cardiovascular disease is the leading cause of death in women. The ‘Estudio Epidemiologico de la Mujer’ (EEM) study aimed to explore obesity, diabetes and diabesity in 3500 women over 18 years old. EEM is a cross-sectional epidemiological and multidisciplinary study in seventy consulting rooms of gynecology from twenty two Venezuelan provinces. Hypertension, hypercholesterolemia and metabolic syndrome defined according to NCEP-ATPIII, were surveyed among other cardiovascular risk factors. Cardiologists, gynecologists and endocrinologists participated as investigators in this study. We present the results of 10% of the sample collected to date. Mean (±s.d) age of the participants was 42.25 (13.41) years The prevalence of Obesity and Diabetes was 23.55% (95% CI: 19.64–27.45) and 3.94% (95% CI: 1.92–5.97) respectively. Diabetes was present in 7.14% of obese women. Obesity was detected in 42.86% of diabetic women. Patients with ‘Diabesity’ had higher prevalence of hypertension (83.3%, P = 0.017), hypercholesterolemia (66.7%, P = 0.032) and metabolic syndrome (83.3%, P = 0.000). The prevalence of ‘Diabesity’ and its components was substantial across Venezuelan women. EEM study findings, including evidence of the association of ‘Diabesity’ with hypertension, hypercholesterolemia and metabolic syndrome, should inform appropriate clinical and public health interventions.

DOI: 10.1530/endoabs.32.P779
Chronic inflammation. Adiponectin is widely distributed within each BMI group. It appears to be a good marker of obesity-induced chronic inflammation. The prevalence of obesity is increasing in the UK. Obesity in pregnancy is associated with various maternal and fetal complications. In the latest CMACH (2011) report, 30% of maternal deaths were associated with obesity. Appropriate antenatal interactions between practitioners and patients are crucial to ensure behaviours are adopted to minimise these risks.

Materials and methodology
An audit was performed comparing practice against CNST Criterion 10: obesity. Thirty sets of notes were randomly selected; ten from each BMI class.

Results
All of the patients had BMI’s recorded in the notes and were booked for appropriate maternity based care. However, only 3 out of 30 patients (10%) were explained the antenatal and intrapartum risks associated with obesity in pregnancy.

Discussion
A complex interaction exists between the appropriate balance between medical obligations and moral issues when communicating with obese patients. The media portrayal of obesity as a moral failure has resulted in discrimination towards such patients and consequent difficulty in engaging in sensitive conversations about potentially serious complications. Honest and open consultations, addressing responsibility and control, but without blame, are essential to invoke behavioural change. Adopting such behaviours antenatally is essential to minimise the significant risks associated with obesity in pregnancy.

DOI: 10.1530/endoabs.32.P780

Circulating adiponectin as marker of obesity-induced chronic low grade inflammation
Eirine Dermitsaki, Pavlina Avgoustinaki, Maria Venihaki, Christos Tsatsanis & Andrew Margioris
School of Medicine, University of Crete, Heraklion, Crete, Greece.

Introduction
Obesity lowers adiponectin levels. Adiponectin has anti-inflammatory effects. It has been suggested that the lower levels of adiponectin in obesity results in chronic low grade inflammation (CLGI). Aim of this study was to examine if plasma adiponectin is a valid marker of CLGI in normal weight, overweight and obesity.

Materials and methodology
We measured adiponectin, markers of CLGI (CRP, SAA, ESR), insulin resistance and lipids. Body fat was estimated by DXA and BIA.

Methods
i) Adiponectin was widely distributed within each BMI group. ii) The levels of makers of inflammatory and insulin resistance were progressively and significantly elevated in parallel to the increased BMI. iii) In our combined population, adiponectin was significantly and negatively correlated to BMI, lipids and body fat while no correlation was evident with markers of CLGI. iv) After adjusting for BMI, a positive and moderate correlation between adiponectin and body fat was evident only in the obese. v) The distribution of adiponectin within each BMI group was wide and overlapping the three BMI groups its median value being 10.9 μg/ml. vi) This phenomenon was not due to higher concentrations of adiponectin in the females since it was apparent in the males. vii) Adiponectin levels in each BMI group were separated into quartiles which revealed: a significant reverse association of adiponectin with total and leg fat mass, a weak correlation between adiponectin levels and markers of CLGI, and a significant correlation to insulin resistance.

Discussion
Adiponectin is widely distributed within each BMI group. It appears to be a good marker of adiposity and insulin resistance but not a valid marker of obesity-induced chronic inflammation.

DOI: 10.1530/endoabs.32.P781

Prevalence of obesity, diabetes and prediabetes in Tirana, the capital of Albania 2010–2011
Florian Toti, Luftime Bruka, Matilda Kelmendi, Luljeta Cakerri & Agron Ylli
Department of Endocrinology and Metabolic Diseases, University Hospital Center ‘Mother Theresa’, Tirana, Albania.

Introduction
Obesity and diabetes are strongly associated as causes of morbi-mortality in developing countries. The aim of our study was to evaluate the prevalence of overweight, obesity and undiagnosed diabetes in Tirana district, where 1/4 of the total population lives.

Method
Anthropometric and capillary glucose measures for healthy people unknown of diabetes. Diabetes fasting anamnesis, HTA treatment and smoking were included in the questionnaire.

Results
3316 persons included in the study. M/F 1755/1561 (52.9%), mean age 53.4 ± 12.02 years, mean BMI 28.3 ± 1.9 kg/m². Prevalence of Obesity was 23.2% equally present M/F 23.4/23.1%, overweight 46.5%, more present in men 49.4/41.2% (P < 0.05). Obesity was more frequent in group 40–60 years old – 27.25%, but 15.9% for the group 30–40 years old. Central obesity was present in 67.7% of cases, more frequent in women 79.9 vs 50.1% (P < 0.01). Prevalence of undiagnosed Diabetes was 3.5%, IFG 14.5%, IGT 10.6%. Diabetes was more frequent in the groups 20–30 years (5.41%) and 50–60 years 4.32%. The patient diagnosed with Diabetes had the tendency to be more overweight 53.3 vs 44.2%, to have more familiar anamnesis for diabetes (P < 0.01) and suffer from HTA (P < 0.05), but not obese 20 vs 21.5%. IFG and IGT were more frequent in the group 50–60 years old.

Conclusions
Prevalence of obesity, diabetes, and prediabetes is very high in Albania, especially in younger age group. It is important to raise the awareness and counseling of younger population about healthy living habits and weight control, as well as the frequency of controlling blood glucose level.

DOI: 10.1530/endoabs.32.P782
P784

PTH one year after gastric bypass in morbidly obese patients
Snezana Polovina, Dragana Micic, Jelena Gligorijevic, Mirjana Sumarac-Dumanovic, Goran Cuvovic, Danica Stamenkovic-Pejkovic, Jelena Milin, Dusan Micic & Danka Jeremic

1Clinic for Endocrinology, Diabetes and Diseases of Metabolism, Clinical Center of Serbia, Belgrade, Serbia; 2Dietary unit, Clinical Center of Serbia, Belgrade, Serbia; 3Emergency Center, Clinical Center of Serbia, Belgrade, Serbia.

Introduction

After gastric bypass, gastric secretion decreased and resorption of minerals and vitamins may be compromised. Lower resorption of serum calcium and vitamin D could stimulate PTH secretion after restrictive and malabsorptive bariatric procedures. Methods

We have measured serum calcium, D vitamin and PTH in patients (n=50, 17 males and 33 females) 6 and 12 months after R en Y gastric bypass, 38.6 ± 12.6 years of age, with BMI 43 ± 9.2 kg/m². Exclusion criteria were thyroid dysfunction and previous primary or secondary osteoporosis. All patients were supplemented with calcium and vitamin D after bariatric surgery under the recommendations from European guideline for bariatric surgery. The supplements were contained 1250 mg of calcium carbonate and 400 IU of vitamin D in the first 2 months after surgery, and 600 mg of calcium citrate and 200 IU of vitamin D from the 3rd month to 1 year after gastric bypass.

Results

Serum calcium was 2.39 ± 0.03 mmol/l after 6 months and 2.41 ± 0.10 mmol/l after 12 months. The difference of −0.02 mmol/l was no significant (P = 0.83). The serum level of vitamin D was 53.79 ± 24.60 ng/ml after 6 months and 46.73 ± 15.83 ng/ml after 12 months. The difference of 7.02 was no significant (P = 1.34). After 6 months the mean PTH was 56.28 ± 25.429 pg/ml, after 12 months 46.646 ± 21.056 pg/ml, and that difference also was no significant (P = 0.94).

Conclusion

One year after gastric bypass there was no significant changes in serum calcium, vitamin D and PTH level. Dietary supplements with calcium carbonate and D vitamin in the first 2 months, and with calcium citrate and vitamin D after that period in obese patients after restrictive and malabsorptive bariatric surgery procedures, is sufficient supplementation model without increasing PTH and risk for bone resorption.

DOI: 10.1530/endoabs.32.P784

P785

Neck circumference association with metabolic risk factors in patients undergoing neck surgery
Danijela Grizelj, Vlatka Pandzic Jaksic, Drago Boscic, Marko Ajduk, Ivan Ozegovic, Predrag Pavic, Marin Subaric & Ozren Jaksic

Dubrava University Hospital, Zagreb, Croatia.

Adipose tissue distribution is one of the key determinants of metabolic dysfunction in obesity. Several large scale studies found that enlarged neck circumference is independently associated with cardiovascular risk.

The aim of this study was to examine the association of neck circumference with metabolic risk factors in patients undergoing neck surgery.

In 36 patients undergoing thyroid or vascular neck surgery we determined serum levels of insulin, glucose, triglycerides, HDL-cholesterol and C-reactive protein. We performed anthropometric measurements (body weight and height, BMI, waist circumference and neck circumference) and body composition analysis. We also evaluated carotid intima-media thickness and the presence of carotid plaques. Study participants did not have any inflammatory or malignant diseases.

They did not have any thyroid or other specific neck mass that could particularly enlarge neck circumference.

Statistically significant positive correlations were found between neck circumference, other anthropometric measures of obesity and body fat mass (P < 0.05). Neck circumference also positively correlated with levels of insulin, glucose and triglycerides, but negatively with HDL-cholesterol (P < 0.05). Neck circumference was associated with carotid intima-media thickness (P < 0.05). Patients with carotid plaques had significantly larger neck circumference (P < 0.05). In correlations with metabolic risk factors, neck circumference did not show any difference from waist circumference.

These preliminary results support the hypothesis that at least part of neck adipose tissue my be related to the metabolically adverse impact similar to ectopic fat. Samples of adipose tissue taken during neck surgery might bring further information about this particular fat depot. In that context we plan to proceed with investigations on neck adipose tissue samples from subcutaneous and perivascular locations.

DOI: 10.1530/endoabs.32.P785

P786

Rapid reversal of hyperglycemia despite modest weight loss in a patient post gastric bypass surgery: a case report and review of the literature
Abel Weiliang Chen, Samuel Shang Ming Lee, Wei Feng Lee, Gabriel Liu, Yuan Chen, Cheng Jye Seow & Hong Tar Khor

Tan Tock Seng Hospital, Singapore, Singapore.

Background

Bariatric surgery has been shown to decrease insulin requirements even before significant weight loss has occurred. We report a patient with marked improvement in glycemic control despite modest weight loss post bariatric surgery.

Case presentation

A 47 years old Chinese man with obesity (weight 90 kg, BMI 31.2), hypertension, hyperlipidemia and type 2 diabetes mellitus diagnosed in 2005 is on follow up with our endocrine clinic. Despite compliance to more than 200 units of insulin a day, his glycemic control remained poor with a HbA1c persistently more than 10%. This is largely attributed to insulin resistance and dietary indiscretion.

He underwent laparoscopic Roux-en-Y gastric bypass in mid 2012. Post-operatively, he experienced a total of 14 kg weight loss over 6 months. His HbA1c fell from 11.4 to 6.7% (within 4 months). All his diabetic and cholesterol lowering medications have been stopped.

Discussion

Resolution or remission of T2DM has been well documented following bariatric surgery in obese patients. This phenomenon is well reported after significant weight reduction. In this case study, the actual achieved weight loss was modest (15.6 vs 45.1% estimated weight loss in other demographically similar subjects), yet the glycemic control was comparable to similar subjects who lost much more weight in the same time period. This rapid reversal of hyperglycemia is not well understood and could partly be explained by improved beta cell function and insulin sensitivity following malabsorptive bariatric surgery. These outcomes have been linked to enhanced incretin responses along the gastroenteroinsular axis facilitating these improvements in glucoregulation.

DOI: 10.1530/endoabs.32.P786

P787

Insulin resistance at obesity and diabetes
Victoria Lesyukova, Kulyash Zekenova, Irina Savasteeva, Elena Bondareva, Elena Smitsarenko & Nina Komisarova

The Republican Research Centre for Radiation Medicine and Human Ecology, Gomel, Belarus.

The urgency of metabolic syndrome problem in modern medicine is caused by metabolic syndrome prevalence in the general population of 14–24%.

The metabolic syndrome plays an essential role in cardiovascular diseases development acceleration. Components are abdominal–visceral obesity, insulin resistance, hyperinsulinemia, dyslipidemia, arterial hypertension and carbohydrate metabolism disorder.

Aim

Frequency estimate 2nd type diabetes and insulin resistance in obesity

Materials and methods

For metabolic syndrome severity and obesity degree verification the BMI was calculated. Immunoreactive insulin level was defined by the immunofermeral analysis metod. The insulinresistance was defined by HOMA-index calculation.
P788
Lean mass and fat mass distribution in Ukrainian women with metabolic syndrome in postmenopausal period

Vladyslav Povoroznyuk1, Larysa Martyntyuk2 & Lilya Martyntyuk1,2
1Institute of Gerontology NAMS Ukraine, Kyiv, Ukraine; 2I. Hobachevsky

Objective
Menopause-related changes in female body are associated with the greater risk of metabolic syndrome (MS), which includes obesity, dyslipidemia, impaired glucose tolerance, hypertension.

Aim
The purpose of our study was to reveal peculiarities of fat and lean mass distribution between postmenopausal women with abdominal obesity and without MS.

Methods
The sample consisted of 43 postmenopausal 60–69 years old women (age: mean = 64.8; s.d. = 4.0); duration of menopause: mean = 14.5; s.d. = 9.9). The diagnosis of MS was considered according to IDF (2005) criteria. Lean and fat mass distribution were measured by dual-energy X-ray absoriometry, and were compared for the cohorts with and without MS. Data were analyzed using Statistical Package 6.0 (Statsoft).

Results
Findings revealed that 24 (55.8%) of postmenopausal women had MS. In patients with and without MS compared, fat mass was higher in the former group (41248.25 ± 2001.81 g and 2798.15 ± 282.79 kg respectively; F = 9.06; P = 0.004). Lean mass comparing didn’t show significant differences in female with and without MS (42548.0 ± 1239.18 kg and 40667.53 ± 1223.78 kg respectively; F = 1.1; P = 0.29) and at different body regions also.

Conclusion
These findings suggest that in postmenopausal women with MS there is prevalence of fat mass without increasing of lean mass quantity in compare to female with abdominal obesity without MS.

DOI: 10.1530/endoabs.32.P788

P789
Lean and fat mass in Ukrainian women of different age

Vladyslav Povoroznyuk & Nataliia Dzorych
Institute of Gerontology NAMS Ukraine, Kyiv, Ukraine.

Aim
The aim of this study is evaluating of body composition and frequency of sarcopenia in women depending on age.

Materials and methods
We’ve examined 8637 women aged 20–89 years (mean age – 56.7 ± 0.14 years; mean height – 162.5 ± 0.07 cm; mean weight – 73.5 ± 0.16 kg). The patients were divided into two groups depending on age: 20–24 (n = 143), 25–29 (n = 209), 30–34 (n = 271), 35–39 (n = 326), 40–44 (n = 419), 45–49 (n = 794), 50–54 (n = 1292), 55–59 (n = 1534), 60–64 (n = 1193), 65–69 (n = 943), 70–74 (n = 877), 75–79 (n = 384), 80–84 (n = 204) and 85–89 years (n = 48). Lean and fat masses and total body, lumbar spine, femoral neck bone, forearm bone mineral density (BMD) were measured by DXA using a densitometer Prodigy, GE.

Results
We have found the significantly differences of fat and lean masses in women with age:

- fat mass: 20–24 years – 18 630.12 g; 25–29 years – 18 630.12 g; 30–34 years – 19 201.00 g; 35–39 years – 21 528.15 g; 40–44 years – 24 611.77 g; 45–49 years – 27 501.54 g; 50–54 years – 27 501.54 g; 55–59 years – 29 909.92 g; 60–64 years – 31 600.27 g; 65–69 years – 33 506.25 g; 70–74 years – 33 155.54 g; 75–79 years – 32 284.86 g; 80–84 years – 30 595.53 g; 85–89 years – 30 303.68 g; F = 83.19; P < 0.0000001;
- lean mass: 20–24 years – 37 271.57 g; 25–29 years – 37 954.09 g; 30–34 years – 39 019.72 g; 35–39 years – 39 928.62 g; 40–44 years – 40 929.67 g; 45–49 years – 41 407.19 g; 50–54 years – 41 936.27 g; 55–59 years – 42 564.79 g; 60–64 years – 42 519.73 g; 65–69 years – 41 758.95 g; 70–74 years – 41 233.77 g; 75–79 years – 41 105.52 g; 80–84 years – 40 308.00 g; 85–89 years – 38 454.61 g; F = 29.15; P < 0.0000001.

Frequency of sarcopenia in women aged 65 years and older was 7% (women aged 65–69 years (n = 943) – 7.6% (n = 72), 70–74 years (n = 877) – 6.1% (n = 54), 75–79 years (n = 384) – 6.3% (n = 24), 80–84 years (n = 204) – 6.9% (n = 14), 85–89 years (n = 48) – 10.4% (n = 5).

Conclusion
Fat and lean masses were significantly decreased with age. The maximal accumulation of fat and lean masses was in women aged 50–59 years. Frequency of sarcopenia in women aged 65 years and older was 7%.

DOI: 10.1530/endoabs.32.P789

P790
Dieting attitudes among college students in Romania

Veronica Mocanu
Grigore T. Popa University of Medicine and Pharmacy, Iasi, Romania.

Objectives
The aim of the study was to assess the eating attitudes and behaviors, including weight concerns and dieting behavior, among medical college students.

Methods
The sample consisted of 70 undergraduate students from the School of Medicine, Iasi, Romania, 22 males and 48 females, aged 25 ± 2 years. Eating-related behaviors were measured using the EAT-26 questionnaire. Study of food intake and physical activity was conducted using a questionnaire, that included anthropometric measures, food frequency and the level of physical activity. We calculated BMI from students 'self-reported height and weight.

Results
The mean BMI was 22.5 ± 4 kg/m², ranging from 16.2 to 31.7 kg/m². Approximately 15% of the students were overweight, and 7% were obese. Another 17% were underweight, and the remainder (63%) were of healthy weight. The results showed that 7% of the students had a positive EAT-26 score (>20) and 10% scored higher on the dieting subscale. The results demonstrated a high prevalence of disturbed eating attitudes and behaviors among college students. Our analysis showed that students with dieting behavior report excessive exercising and consuming less cereals and meat and more legumes as compared to non-dieting behavior group.

Conclusion
The prevalence of eating disorders may be increasing in our country, because the young girls experiencing more cultural imperatives for thinness.

DOI: 10.1530/endoabs.32.P790
Paediatric endocrinology

P791

GH treated children with IGF1 deficiency and excluded GH insensitivity despite normal GH secretion may attain similar final height as children with GH deficiency
Joanna Smyczynska1, Andrzej Lewinski2, Renata Stawerska1 & Maciej Hilczer1,2
1Department of Pediatric Endocrinology, Medical University of Lodz, Lodz, Poland; 2Department of Endocrinology and Metabolic Diseases, Research Institute, Polish Mother’s Memorial Hospital, Lodz, Poland.

Introduction.
The diagnosis of GH deficiency (GHD) is based on decreased GH peak in stimulating tests (GHST). Recently, GHD has been re-defined as secondary IGF1 deficiency (IGFD). However, IGF1 may increase during GH therapy in the patients with normal GH peak in GHST, suggesting a diagnosis of non-primary IGFD (npIGFD).

The aim of the study was to compare GH therapy effectiveness in children with GHD and with npIGFD (responding to GH administration despite normal results of GHST).

Patients and methods
The analysis comprised 300 children (228 boys and 72 girls), with short stature and/or were GHD (GHD) - GH peak <5 ng/ml, height SDS at GH therapy onset (HoSDS) – 3.20 ± 0.87 (mean ± s.d.), n = 43; ii) partial GH (pGHD) – GH peak 5–10 ng/ml, HoSDS – 3.06 ± 0.78, n = 188; and iii) npIGFD – GH peak > 10 ng/ml, decreased IGF1 (i.e. IGF1 SDS < -1.0), increasing significantly during generation test, HoSDS – 3.11 ± 0.70, n = 69.

All the patients were treated with GH in a dose of 0.18 G/m2 per week up to the attainment of final height (FH). Selected auxological indices of GH therapy effectiveness were compared: i) FH SDS for age and sex; ii) FH SDS corrected by target height SDS (corrFH SDS); and iii) an increase of FH SDS with respect to HoSDS (ΔFHSDS).

Results
The attained FH SDS was slightly worse in npIGFD (−1.48 ± 0.89) than in GHD (−1.38 ± 1.25) but better than in pGHD (−1.62 ± 0.83), while corrFH SDS was similar in all the Groups (−0.32 ± 0.87 vs -0.38 ± 1.09 vs -0.39 ± 0.97 respectively). Moreover, ΔFHSDS was similar in npIGFD (1.62 ± 0.88) and pGHD (1.68 ± 1.56), being even better than in pGHD (1.42 ± 0.95). All the differences among the groups were insignificant.

Conclusion
It seems that GH therapy should be considered in children with IGFD, responding to GH despite normal results of GHST, because the efficacy of treatment is similar as in GHD.

DOI: 10.1530/endoabs.32.P791

P792

Reference curves for body fat (%) for Danish children evaluated by skinfolds and dual-energy X-ray absorptiometry
Christine Wohlfahrt-Jeje, Jeanette Tinggaard, Annette Mouritsen, Casper Hagen, Mikkel Grunnet, Katrine Tefre de Renzy-Martin, Malene Boas, Jørgen Holm Pedersen & Katharina M Main
Rigshospitalet, Copenhagen, Denmark.

Background
Over the last 80 years body composition of young people have changed towards increased fatness. Whole body fat percentage (%BF) derived from dual energy X-ray absorptiometry (DXA) scans are (although often not available) widely recognized as a better measure of fatness than BMI.

Objective
We aimed to provide reference materials for %BF of healthy Danish children evaluated by skinfold measurements and DXA and to compare sensitivity and specificity of different assessments of excess fatness.

Methods
Height, weight, and skinfolds, were measured in a large longitudinal cohort of Danish children from the Copenhagen area (n=2647,12792 examinations) between birth and 14 years. DXA scans were performed once at age 6–14 (n=1200). We calculated %BF from skinfold-measurements (Slaughter equation), evaluated number of overweight by BMI (Cole criteria) and evaluated increased fatness by DXA (using adult cut off values: males: 25%, females: 30%).

Results
Reference curves for %BF were constructed for boys and girls with generally higher values for girls and with broad intervals between +1s.d. and +2s.d. in both genders.

%BF from skinfolds were significantly lower (mean difference 13%) but correlated strongly (r=0.88) with DXA %BF, (and with similar Z-scores). BMI Z-score also correlated positively with DXA %BF (r=0.74), but a child with a normal BMI for gender and age (~1<BMI Z-score<1) could have a DXA %BF between 6 and 7. When applying adult cut off values for DXA %BF = +1s.d. to identify children with excess fatness, only half of them were identified using BMI/Cole criteria (specificity of 99, but sensitivity of 50.5). Using %BF from skinfolds gave a specificity of 94.4 and sensitivity of 75.3.

Conclusions
Normal weight children may have too much fat. %BF derived from skinfolds measurements had a higher sensitivity than BMI when compared to the DXA when identifying children with excess fat.

DOI: 10.1530/endoabs.32.P792

P793

Abnormalities in growth and in the IGF system can be associated to permanent chronic inflammatory process in HIV-infected children independently of clinical control
Marcelo Ruiz, Soraya Milani, Rodrigo Custódio, Bento Negrini, Maria Célia Cervi & Carlos Martinelli
School of Medicine of Ribeirão Preto-USP, Ribeirão Preto, São Paulo, Brazil.

Background
HIV-infected paediatric patients usually show impaired growth. Data reporting abnormalities in GH–IGF–IGFBPs system are scarce and inconclusive.

Aim
To analyse blood concentration of the major components of IGF–IGFBPs system in these children and compare them to growth parameters and to cytokines levels.

Methods
prepubertal HIV-infected children, aged 8.2 ± 1.7 years, were evaluated every 6 months during 1 year when anthropometric data and blood samples were collected for IGFs, IGFBPs, cytokines and viral load (VL) determinations. Thirty healthy prepubertal children were studied as controls. IGF1, IGF2, IGFBP3 and IGFBP1 were determined by ELISA and IGFBP2 and IGFBP4 by western-ligand blotting (WLB). Interleukin 6 (IL6) and tumoral necrosis factor α (TNFa) were determined by Luminex. We defined VL < 5.000 and VL > 5.000 copies/ml as good (GC) and poor (PC) disease control respectively.

Results
BMI in HIV-infected children was similar to controls. Height was lower in HIV-children than in controls (P<0.001). Serum IGF1, IGFBP3 were similar in PC and in GC but lower than in controls. IGFBP1 and IGFBP4 levels were similar among PC, GC and controls. IGFBP2 levels were higher in PC than in GC. IL6 and TNFa concentrations were similar in PC and in GC but higher than in controls, indicating a permanent chronic inflammatory process in HIV-infected children. No significant correlation was observed between IL6 or TNFa and IGF1, IGFBP2 or IGFBP3. However, IGFBP1 levels were significantly lower (<0.58 ng/ml) in samples with TNFa > 24 pg/ml (P=0.0006) or IL6 > 3.8 pg/ml (P=0.05).

Conclusion
HIV-children present poor growth comparatively to healthy children. The poor growth may be explained by alterations in IGF–IGFBPs system that reduces IGF bioavailability/activity during good or poor disease control. The permanent and chronic inflammatory process may contribute to IGF–IGFBPs alterations.

DOI: 10.1530/endoabs.32.P793
P794

Unaltered sex steroid levels, but elevated serum IGF1 in healthy boys with pubertal gynaecomastia
Mikkeli Grunnet Mieiritz, Kaspar Sorensen, Lise Akslaade, Annette Mourisen, Casper P Hagen & Anders Juul
Department of Growth and Reproduction, Rigshospitalet, Copenhagen, Denmark.

Introduction
The presence of glandular breast tissue in males around puberty, pubertal gynaecomastia, is a very common (40–60%) condition although the aetiology behind is poorly understood. It is generally accepted that pubertal gynaecomastia is caused by an excess of estrogens and/or a deficit of androgens. However, other hormones such as prolactin, GH and IGF1 may also affect ductal growth of the breast.

Design
A cross-sectional study of 518 healthy Danish school boys (aged 6.1–19.8 years) as a part of the COPENHAGEN Puberty Study. Anthropometry and pubertal stages (PH1–6 and G1–5) were evaluated, and the presence of gynaecomastia was assessed. Body fat percentage was calculated by means of skin folds and impedance. Non-fasting blood samples were analysed for FSH, LH, testosterone, SHBG, estradiol, IGF1, IGFBP3 and prolactin. Furthermore free-testosterone, FAL and E2/testosterone were calculated.

Results
We found that boys with gynaecomastia had significantly higher height, weight, hip circumference, testis volume, genital and pubic hair stages, levels of FSH, LH, estradiol, testosterone and IGF1, but lower levels of SHBG. FSH (P<0.029) and IGF1 (P<0.003) remained significantly higher in boys with gynaecomastia even after adjustment for age and pubertal stage. We did not find any significant difference in the sex steroid levels or in estradiol/testosterone-ratio, FAL, or free testosterone.

Conclusion
We found that Danish boys with gynaecomastia had significantly higher serum IGF1 levels compared to boys without palpable gynaecomastia at the time of investigation. No other significant hormonal differences were seen. We suggest that the GH–IGF1 axis may be involved in the pathogenesis of pubertal gynaecomastia.

DOI: 10.1530/endoabs.32.P794

P795

Metabolic syndrome in adolescents and young adults with childhood-onset GH deficiency
Joanna Owsiencinska1, Katarzyna Ziora1, Magdalena Pys-Spychala2, Agnieszka Szymiałka1 & Agata Mikolajczak3
1Department of Paediatrics, Medical University of Silesia in Katowice, Zabrze, Poland; 2Department of Paediatrics, District Hospital, Strzelce Opolskie, Poland.

Introduction
There is only few data on metabolic syndrome occurrence in young patients with childhood-onset GH deficiency (CO-GHD), especially its partial form.

Aim
The aim of this study was the assessment of the metabolic syndrome criteria (according to IDF 2007) occurrence in adolescents and young adults with CO-GHD and evaluation of their correlations with the degree of GH/IGF-1 axis function impairment.

Subjects and methods
The study was performed in a group of total 122 subjects aged 16–25 years. Based on current peak serum GH concentrations in insulin tolerance test (ITT) patients were qualified for one of the following groups: i) severe GH deficiency (GHD; peak GH < 5.0 ng/ml, n = 26). ii) partial GH (PGHD; peak GH 5.0–10.0 ng/ml, n = 22), iii) normal GH secretion (NGH; peak GH > 10.0 ng/ml, n = 28). iv) healthy subjects (H; n = 46). Following examinations were performed: i) anthropometric measurements (body mass, height, hip and waist circumference), ii) blood pressure iii) serum glucose, insulin, total, LDL and HDL cholesterol, triglycerides, IGF1, iv) HOMA-IR was calculated.

Results
WHR was significantly (P<0.01) higher in GHD (0.82) as well as in PGHD (0.78) in comparison with NGH (0.73) and H (0.73) subjects. We observed significantly elevated (P<0.05) total and LDL-cholesterol, triglycerides and hsCRP in GH, but not in PGHD compared to NGH or H groups. There were no differences in fasting glucose, insulin and HOMA-IR values between the examined subjects. Metabolic syndrome has been diagnosed in four NGH patients (15.4%). Significant (P<0.05) negative correlations between the peak ITT GH concentrations and hsCRP (r = -0.51), total (r = -0.43) and LDL-cholesterol (r = -0.38) and triglycerides (r = -0.28) were observed. Serum IGF1 correlated negatively with hsCRP (r = -0.44), glucose (r = -0.43) and HOMA-IR (r = -0.31) and positively with insulin (r = 0.29).

Conclusion
i) Metabolic syndrome is significantly more frequent in adolescents and adults with GHD. ii) Partial CO-GHD is not associated with metabolic disturbances in our patients.

DOI: 10.1530/endoabs.32.P795

P796

Premature pubarche: distinguishing between nonclassic congenital adrenal hyperplasia and idiopathic premature adrenarche
Ester Pereira, Joana Caetano, Rita Cardoso, Sara Ferreira, Lília Santos, Marta Ferreira, Beatriz Vale, Isabel Dinis & Alice Mirante
Unit of Endocrinology, Diabetes and Growth, Hospital Pediátrico do Centro Hospitalar e Universitário de Coimbra, EPE, Coimbra, Portugal.

Introduction
Premature pubarche (PP) is most often related to idiopathic premature adrenarche (IPA). However, it is a diagnosis of exclusion and differential diagnosis must include milder and nonclassic variants of congenital adrenal hyperplasia (CAH).

Materials and methods
A retrospective study was conducted including children seen for PP between 2001 and 2011 with baseline blood sampling for DHEAS, androstenedione, 17OHP and free testosterone and a follow up of at least 1 year. Patients were considered to have CAH if their 17OHP level was ≥ 2.0 mg/ml and CAH was confirmed by mutational analysis of the CYP21 gene. Exclusion criteria were: neonatal onset, concomitant clinical signs of central puberty and genetic syndromes. Statistical analysis was done using SPSS 19th (P<0.05).

Results
Fifty-three children with PP were included: 6 had CAH (11.3%) and 47 were classified as IPA (88.7%). Pubic hair onset was reported by the parents at 4.9 ± 2.2 and 4.9 ± 1.6 years (P=0.940) and age at the first appointment was 7.1 ± 1.0 years and 6.9 ± 1.5 (P=0.692) in CAH and IPA respectively. There was no difference on stature SDS and BMI-SDS at the first appointment and after one year. Progression of pubic hair Tanner stage in the first year also didn’t differ between the two groups. Growth velocity SDS was 1.34 ± 0.76 in CAH and 0.75 ± 1.06 in IPA (P=0.195). Bone age was advanced 1.9 ± 1.3 years in CAH and 1.1 ± 1.3 years in IPA (P=0.175). Besides 17OHP, also free testosterone was higher in the CAH group (P=0.005).

Conclusions
CAH cannot be distinguished from IPA on a clinical basis. Evaluation of androgens is essential to make the differential diagnosis in a child with PP.

DOI: 10.1530/endoabs.32.P796

P797

Improvement in metabolic control of type 1 diabetes mellitus in a tertiary unit: 2005 vs 2012
Joana Caetano, Sara Ferreira, Ester Pereira, Marta Ferreira, Helena Lourenço, Lina Aveiro, Nanci Batista, Filomena Freitas, Luísa Simão, Rita Cardoso, Isabel Dinis & Alice Mirante
Unit of Endocrinology, Diabetes and Growth, Hospital Pediátrico do Centro Hospitalar e Universitário de Coimbra, EPE, Coimbra, Portugal.

Introduction
To define the main predictors of metabolic control in children and adolescents and evaluate its improvement along the years.

Methods
We included children and adolescents with 1DM, with more than two years of disease. Data were collected at 2005 and at 2012. Sex, age and severity at diagnosis, therapy in the last year, age at onset of multiple daily insulin injections (MDII) and continuous subcutaneous insulin infusion (CSII), number of group educational sessions, insulin daily doses (IDD) and mean HbA1c along last year were collected. Three groups were defined to evaluate metabolic control (1, HbA1c ≤ 7.5%; 2, HbA1c 7.5–9%; 3, HbA1c ≥ 9%). Statistic analysis was performed with SPSS®.
Results
We included 243 children with IDM (107 in 2005 and 136 in 2012). There were no differences in sex, age at diagnosis (6.0 ± 3.3 vs 6.6 ± 3.6 years) or duration of illness (6.8 ± 3.3 vs 6.2 ± 3.6 years). Severity at diagnosis was higher in 2005 (P=0.021). In 2005, 34.6% were in conventional therapy and 65.4% in MDII. In 2012, all children were in intensive therapy since diagnosis (75% MDII and 25% CSII). Comparing data from 2005 to 2012, we found statistical difference in number of group educational sessions (1.6 ± 0.9 vs 4.8 ± 2.5, P<0.001), duration of MDII (1.8 ± 2.2 vs 3.5 ± 1.1, P=0.001), IDD (1.04 ± 0.27 vs 0.91 ± 0.22 IU/kg/d, P<0.001), mean HbA1c in the last year (8.7 ± 1.3% vs 7.7 ± 1.0%, P<0.001), and groups of HbA1c (group 1=17.8%, 2=52.3%, 3=29.9%, vs group1=47.1%, 2=45.6%, 3=7.4%, P<0.001). In 2012, the children in group 1 had started MDII at younger age (P=0.04) with lower IDD (P=0.02) and had more children in CSII (P<0.001); children in group 3 were older (P=0.04).

Conclusion
There was a clear improvement in metabolic control from 2005 to 2012. The main predictors of greater metabolic control were early onset of MDII and CSII and increase of educational sessions. This reconfirms the advantage of intensive insulin therapy since diagnosis.

DOI: 10.1530/endoabs.32.P797

P798
Subclinical hypothyroidism in obese children: the influence of l-thyroxin treatment on metabolic comorbidities and a success of dietary therapy
Paweł Matusik, Aleksandra Januszek-Trzciakowska & Ewa Malecka-Tendera
Department of Pediatrics, Pediatric Endocrinology and Diabetes, Medical University of Silesia, Katowice, Poland.

Introduction
Subclinical hypothyroidism (sHT) is defined as elevated level of TSH with normal levels of thyroid hormone. In obese children there is a high frequency of this disturbance. However, the influence of sHT on therapy success and an appearance of metabolic complications in childhood obesity is unclear. Furthermore, the supplementation l-thyroxin (l-T4) in this case seems to be very controversial.

Aim
The aim of this study was to evaluate of sHT appearance and l-T4 treatment influence on metabolic complication and therapy success in obese children.

Materials and methods
Medical records of 55 obese children with sHT diagnosed underwent retrospective analysis. 29 children (group 1) l-T4 treated with mean age 9.8 years and mean BMI - 27.1 kg/m². Not treated group: 26 children with mean age – 10.1 years and BMI – 27.2 kg/m² (group 2). Both groups received dietary and behavioural counselling. Anthropometrical parameters, metabolic complications and efficiency of dietary therapy were analysed in both groups.

Results
In 1 and 2 g respectively 86.2 and 80.8% of children showed up on a check-up visit. There was no significant difference in frequency of metabolic complications between both groups. Proportion of children that obtained the body mass loss was similar (48% in 1 g and 43% in 2 g). The efficiency of therapy presented by delta of BMI Z-score (s.d.) was also comparable (∆ Z-score BMI was respectively -0.55 and -0.63 s.d.). Normalisation of TSH was gained at 62% of children in group not treated with l-T4.

Conclusions
sHT doesn’t decrease the efficiency of dietary therapy in children. The l-T4 treatment of sHT in children has no influence on frequency of metabolic complications and efficiency of therapy. The body mass reduction in obese children with sHT enables the normalisation of TSH without the necessity of pharmacotherapy.

DOI: 10.1530/endoabs.32.P798

P799
Urinary phthalates from 168 girls and boys measured twice a year during a 5-year period: associations with adrenal androgen levels and puberty
Annette Mouriszen, Hanne Frederiksen, Kaspar Sørensen, Lise Aksgaede, Casper Hagen, Niels Erik, Skakkebaek, Katharina M Main, Anna-Maria Andersson & Anders Juul
Department of Growth and Reproduction, Copenhagen, Denmark.

Endocrine Abstracts (2013) Vol 32

Background
Little is known about the possible deleterious effects of phthalate exposure on endogenous sex steroid levels in children.

Design
A longitudinal study.

Materials and methods
168 Healthy children (84 girls) were examined every 6 months for 5 years, with pubertal staging, measurements of serum levels of DHEAS and Δ4-androstone-dione (Adione) and repetitive longitudinal morning urinary measurements of 14 phthalate metabolites, corresponding to seven different phthalate diesters. A geometric mean (GM) excretion of each child was calculated as the GM urinary phthalate amount (ng) per kilogram (kg) body weight in consecutive urine samples.

Results
We found that girls with excretion of the sum of dibutyl phthalate isomers (MBP) and di(2-ethylhexyl) phthalate (DEHP) metabolites above geometric mean (795 and 730 ng/kg respectively) had lower serum levels of DHEAS and Adione, although only statistical significant at 13 years of age. In boys we found that excretion of MBBzP above geometric mean (346 ng/kg/day) was associated with a lower serum level of DHEAS at 11 years of age. A lower age at pubarche was observed in the boys with ‘high’ excretion of the sum of dibutyl phthalate isomers (MBP) metabolites (11.0 vs 12.3 years).

Conclusion
We provided some evidence that excretions of the phthalates, MBP in girls and MBBzP in boys, were negatively associated with adrenal androgen levels. However, the lower androgen levels were not correlated to changes in age at pubarche.

The lower androgen levels in girls in the ‘high’ excretion group of MBP did not appear to influence onset of puberty. However, the boys in the ‘high’ excretion groups of MBP and the maternal sum of correlated phthalates appeared to start puberty earlier than the boys in the ‘low’ excretion group. Our study did not reveal any clues with regard to possible mechanisms, but we speculate that theoretically, phthalates may not just interfere with steroidogenesis but they could also act directly at the hypothalamic-pituitary level.

DOI: 10.1530/endoabs.32.P799

P800
Hormonal and auxological data of the patients with persistent and transient GH deficiency, diagnosed according to different criteria after completion of growth-promoting therapy
Maciej Hilczer1, Joanna Szymczyńska1,2, Renata Stawierska1,2 & Andrzej Lewinski2,3
1Department of Pediatric Endocrinology, Medical University of Lodz, Lodz, Poland; 2Department of Endocrinology and Metabolic Diseases, Research Institute of Polish Mother’s Memorial Hospital, Lodz, Poland; 3Department of Endocrinology and Metabolic Diseases, Medical University of Lodz, Lodz, Poland.

Introduction
In majority of patients with childhood-onset GH deficiency (GHD), normalisation of GH secretion at the attainment of final height (FH) is observed. However, different criteria for GHD diagnosis may be considered. The aim of the study was to compare the auxological and hormonal data of the patients with persistent and transient GHD, diagnosed according to different criteria.

Patients and methods
The analysis comprised 150 patients (117 boys), age 12.5 ± 2.7 years (mean s.d.), with GHD, who completed GH therapy in a dose of 0.18-0.56 mg/kg per week, attained FH and were subjected to re-evaluation of GH secretion in stimulating tests (GH re-test) at the age of 17.3 ± 1.1 years.

In the patients with confirmed and excluded GHD in GH re-test, using the following cut-off levels of GH peak: <3 ng/ml (persistent, severe GHD in adults), <6 ng/ml (GHD in young adults), <10 ng/ml (GHD in children), the following auxological and hormonal data before treatment and indices of GH therapy effectiveness were compared i) height SDS at therapy onset (HoSDS), ii) GH peak and IGF 1 SDS before treatment, iii) FH SDS for age and sex, and iv) increase of FH SDS with respect to HoSDS (ΔHFDSDS).

Results
The patients with GH re-test <6 ng/ml had significantly (P<0.05) lower GH peak (3.9 ± 3.2 ng/ml) and IGF 1 SDS (−1.74 ± 2.83) at therapy onset, together with significantly better FH SDS (−0.39 ± 1.19) and ΔHFSDS (2.98 ± 2.14) than the patients with GH re-test >6 ng/ml (7.7 ± 3.9 ng/ml, −1.26 ± 1.71, −1.51 ± 0.86 and 1.51 ± 0.90 respectively), with no difference in HoSDS (−3.38 ± 1.08 vs −3.05 ± 0.73). There was no significant difference in GH therapy effectiveness in
the patients with GH re-test < 3 and 3–6 ng/mL, as well as between ones with GH re-test 6–10 and > 10 ng/mL.

Conclusion
The cut-off value 6 ng/mL for GH re-test seems to be the most appropriate for diagnosing persistent GHD in the patients who achieved FH.

DOI: 10.1530/endoabs.32.P800

P801
Adipocyte dysfunction in pediatric obesity
Iulia CHERLAN, Suzana VLADOU, Anda CARAGHEORGHEOPOL, Florin ALEXIU, Sorina SCHIPOIR, Mihaela GIURCANEANU, Adriana PADURE, Andreea-Cristiana BREHAR, Cristina DUMITRESCU, Camelia PROCOPIUC & Constantin DUMITRACHE
'C.I.Parhon' National Institute of Endocrinology, Bucharest, Romania.

Background
Obesity is associated with adipocyte dysfunction, characterized by an impaired secretion of adipokines, which leads to a systemic inflammatory status.

Aim
To characterize adipokines' profile in a group of obese children and adolescents.

Method
A case-control study comparing 102 obese children (BMI > 95th percentile; aged 10–18 years) to a group of 43 healthy controls matched for age and pubertal status. Adiponectin, leptin, resistin, TNF-α, AFABP and lipocalin-2 were measured using ELISA method and were correlated with traditional clinical and biochemical biomarkers of the metabolic syndrome (BMI, waist circumference, blood pressure, fasting glycemia and insulinemia, and lipid profile).

Results
The plasmatic levels of leptin, resistin, AFABP, lipocalin-2, and IL6 were significantly higher while the adiponectin plasmatic levels were significantly lower in the obese group compared to the control group; TNF-α was not different between groups. Adiponectin, leptin, AFABP, and resistin were significantly correlated to BMI, blood pressure, and insulin resistance biomarkers (negative correlation for adiponectin, positive correlations for others adipokines); there was also a parallel variation of the previous mentioned adipokines and HDL-cholesterol, positive for adiponectin and negative for leptin, resistin, and AFABP. IL6 and lipocalin-2 were positively correlated only to BMI, while TNF-α was positively correlated to systolic blood pressure.

Conclusions
Pediatric obesity is already associated with an altered production of adipokines, which participates in theogenesis of obesity-associated comorbidities.

DOI: 10.1530/endoabs.32.P801

P802
GnRH analog treatment in children with congenital adrenal hyperplasia complicated by central precocious puberty
Ayla Guven, Ayse Nurcan CEBECI & Suna HANCILI
Pediatric Endocrinology Clinics, Göztepe Education and Research Hospital, Istanbul, Turkey.

Introduction
In children with congenital adrenal hyperplasia (CAH), central precocious puberty (CPP) may occur and this situation may compromise final height. We need to prevent pubertal development in children with CAH.

Method
Ten children with CAH were included in ongoing follow-up study. Nine children underwent GnRH stimulation test. GnRH-a-T was used as 3.75 mg/q 4 weeks and 10.5 mg/q 2 years respectively. Five children have 46,XX karyotype, but one of them was reared as a male. Mean follow-up 4 ± 1.8 years. A significant difference was found between mean BA/CA on admission and at last visit (P = 0.002; r = 0.4933), and between mean BA/CA the beginning of GnRHa-T and at last visit (P = 0.002; r = 0.4453). Mean CA was significantly increased in boys than at the beginning of GnRHa-T (8.37 ± 0.9 vs 5.2 ± 1.3 years; P = 0.032).

Conclusion
GnRHa-T should be considered for augmentation of linear growth in children with CAH complicated with CPP, particularly in children with not too advanced BA for CA.

DOI: 10.1530/endoabs.32.P802

P803
Growth and pubertal development in adolescent male wrestlers
Etem Piskin1, Taner Bayraktaroglu2, Faruk Yamaner1, Mustafa Gumus1 & Kemal Tamer1
1Department of Pediatrics, Faculty of Medicine, Ulenc Ecevit University, Zonguldak, Turkey; 2Division of Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine, Bülent Ecevit University, Zonguldak, Turkey.

Introduction
Adolescence is a crucial period for linear growth, and sports training during this time may have positive or negative effects on some physiological processes as growth. The purpose of this study was to evaluate the effect of intense training during somatic growth on the onset of puberty and growth development in adolescent wrestlers.

Description of methods/design
Fifty adolescent male wrestlers and 21 sedentary healthy male controls aged 13–15 years were selected. The wrestlers were active at a competitive level from five different wrestling schools. The maturity status of subjects and data about the anthropometric characteristics were evaluated. Serum levels of testosterone, DHEA-S, FSH, LH, prolactin, cortisol, IGF1, TSH and free thyroxine (fT4) were determined.

Results
Anthropometric characteristics and puberty levels according to Tanner stage were similar in both groups. Sex hormones and cortisol, IGF1, prolactin levels did not differ statistically but TSH concentrations differed significantly between wrestlers and sedentary control groups (P = 0.015).

Conclusion
The results suggest that training in adolescent male wrestlers did not significantly change resting sex hormones or alter the onset of puberty as determined by assessment of pubertal stages. The wrestlers had lower body fat and greater energy expenditure per week, there were no significant differences in height, weight, or BMI.

DOI: 10.1530/endoabs.32.P803

P804
GH therapy and effect on ovarian function and morphology in short prepubertal SGA girls
Jeanette Tinggaard1, Rikke Beck Jensen1, Karin Sundberg2 & Anders Juul1
1Department of Growth and Reproduction, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; 2Department of Fetal Medicine, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark.

Growth and pubertal development in adolescent male wrestlers
Etem Piskin1, Taner Bayraktaroglu2, Faruk Yamaner1, Mustafa Gumus1 & Kemal Tamer1
1Department of Pediatrics, Faculty of Medicine, Ulenc Ecevit University, Zonguldak, Turkey; 2Division of Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine, Bülent Ecevit University, Zonguldak, Turkey.

Introduction
Adolescence is a crucial period for linear growth, and sports training during this time may have positive or negative effects on some physiological processes as growth. The purpose of this study was to evaluate the effect of intense training during somatic growth on the onset of puberty and growth development in adolescent wrestlers.

Description of methods/design
Fifty adolescent male wrestlers and 21 sedentary healthy male controls aged 13–15 years were selected. The wrestlers were active at a competitive level from five different wrestling schools. The maturity status of subjects and data about the anthropometric characteristics were evaluated. Serum levels of testosterone, DHEA-S, FSH, LH, prolactin, cortisol, IGF1, TSH and free thyroxine (fT4) were determined.

Results
Anthropometric characteristics and puberty levels according to Tanner stage were similar in both groups. Sex hormones and cortisol, IGF1, prolactin levels did not differ statistically but TSH concentrations differed significantly between wrestlers and sedentary control groups (P = 0.015).

Conclusion
The results suggest that training in adolescent male wrestlers did not significantly change resting sex hormones or alter the onset of puberty as determined by assessment of pubertal stages. The wrestlers had lower body fat and greater energy expenditure per week, there were no significant differences in height, weight, or BMI.

DOI: 10.1530/endoabs.32.P803

Growth and pubertal development in adolescent male wrestlers
Etem Piskin1, Taner Bayraktaroglu2, Faruk Yamaner1, Mustafa Gumus1 & Kemal Tamer1
1Department of Pediatrics, Faculty of Medicine, Ulenc Ecevit University, Zonguldak, Turkey; 2Division of Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine, Bülent Ecevit University, Zonguldak, Turkey.

Introduction
Adolescence is a crucial period for linear growth, and sports training during this time may have positive or negative effects on some physiological processes as growth. The purpose of this study was to evaluate the effect of intense training during somatic growth on the onset of puberty and growth development in adolescent wrestlers.

Description of methods/design
Fifty adolescent male wrestlers and 21 sedentary healthy male controls aged 13–15 years were selected. The wrestlers were active at a competitive level from five different wrestling schools. The maturity status of subjects and data about the anthropometric characteristics were evaluated. Serum levels of testosterone, DHEA-S, FSH, LH, prolactin, cortisol, IGF1, TSH and free thyroxine (fT4) were determined.

Results
Anthropometric characteristics and puberty levels according to Tanner stage were similar in both groups. Sex hormones and cortisol, IGF1, prolactin levels did not differ statistically but TSH concentrations differed significantly between wrestlers and sedentary control groups (P = 0.015).

Conclusion
The results suggest that training in adolescent male wrestlers did not significantly change resting sex hormones or alter the onset of puberty as determined by assessment of pubertal stages. The wrestlers had lower body fat and greater energy expenditure per week, there were no significant differences in height, weight, or BMI.

DOI: 10.1530/endoabs.32.P803

Endocrine Abstracts (2013) Vol 32
Background
GH receptors are present in ovaries and GH may have a physiological role for ovarian function and development.

Objective and hypothesis
The objective of this study was to examine pubertal development and ovarian growth and differentiation during GH therapy.

Methods
Clinical characteristics, reproductive hormones and ultrasonographic examination of the internal genitals were determined in 18 prepubertal girls during 3 years of GH therapy in a Danish sub-study of the North European SGA study (NESGAS), a multinational, randomised, longitudinal study of GH therapy in short prepubertal children born SGA.

Results
Median age at baseline was 4.91 years (4.51–7.22). Bone age advanced significantly during 3 years of treatment (P = 0.007), but did not exceed chronological age. Uterine and ovarian volume increased significantly (1.05–1.72 ml, P = 0.033 and 0.43–0.9 ml, P = 0.005 respectively), but remained within the lower reference ranges. Ovarian follicles became visible in 69% compared to 27% before GH therapy (P = 0.025). Precocious puberty was observed in one girl and another girl showed signs of a multicystic ovary.

AMH tended to cluster in the lower part of the reference range, but increased significantly during 3-year of treatment (P = 0.028).

SHBG decreased during the first year of GH therapy (P < 0.001) and remained low, while an increase in androstenedione and DHEAS was found during 3 years (P = 0.043 and P = 0.005 respectively). No cases of precocious pubarche were observed.

Inhibin B increased significantly during the first 3 years of treatment, but no significant changes in FSH, LH, estradiol or inhibin A were found.

Conclusions
GH treatment of short SGA girls can generally be considered safe, but as altered pubertal development and ovarian morphology was observed in 2 out of 18 girls, pubertal development and ovarian function should be monitored during GH therapy.

DOI: 10.1530/endoabs.32.P804

P806
Obesity and thyroid function in children – cross-sectional study
Catarina Limbert¹, Maria Inês Santos¹, Frederico Rosário², Daniela Amaral³, Rosa Pina³, Laura Oliveira² & Luders Lopes³
¹University Hospital Dona Estefânia, Lisbon, Portugal; ²Personalized Care Health Unit, Lisbon, Portugal.

Obesity and thyroid function in children – cross-sectional study.

Background
Obesity in children has been increasing dramatically, with a significant increase in cardiovascular and metabolic diseases risk. The role of thyroid dysfunction has been extensively analyzed in obese adults, but to a limited extent in children.

Aims
To estimate the prevalence of hyperthyrotropinemia in obese children and to analyze the influence of BMI-SDS and TSH in other metabolic variables.

Methods
Retrospective study with data from the first evaluation of obese children in our clinic. Demographic, anthropometric and metabolic variables were studied. Descriptive analysis consisted of frequencies distribution for qualitative variables and mean ± s.d. for continuous variables. For the association between BMI-SDS, thyroid function and other metabolic variables multiple linear regression models were used. A P value ≤ 0.05 was considered for statistical significance.

Results
We obtained data from 348 children with mean age of 11.7 ± 3.1 years and mean BMI-SDS of 2.9 ± 0.7. The prevalence of hyperthyrotropinemia was 8.9% and of homeostasis model assessment-insulin resistance (HOMA-IR) elevation was 69.3%. Children with hyperthyrotropinemia revealed TSH and HOMA-IR significantly higher than those with normal serum values. BMI-SDS was positively correlated with TSH and FT₄, but not with FT₃, which controlled for sex, age and pubertal stage. BMI-SDS and TSH were positively and independently correlated with HOMA-IR, but not with the lipids.

Conclusions
The prevalence of hyperthyrotropinemia was similar to that reported in other studies and appeared to be influenced by metabolic factors other than FT₃ or TRH. Children with hyperthyrotropinemia had significantly higher FT₃ and HOMA-IR. BMI-SDS was positively correlated with TSH, FT₄ and HOMA-IR. TSH and BMI-SDS were positively and independently correlated with HOMA-IR, which suggests that hyperthyrotropinemia might exacerbate insulin resistance in obese children.

DOI: 10.1530/endoabs.32.P806

P807
Final height of a group of patients with congenital adrenal hyperplasia
Martá Ferreira¹, Sonia Santos¹, Elísia Pereira², Beatriz Vale², Rita Cardoso², Isabel Dinis² & Alice Mirante²
¹Hospital de Santo António, Porto, Portugal; ²Hospital Pediátrico de Coimbra, Coimbra, Portugal.

Introduction
The final height of children with congenital adrenal hyperplasia (CAH) seems to be compromised. That can happen because of the disease itself or because an excessive dose of corticoids used during treatment. This work evaluates the final stature SDS of a group of patients with CAH and correlates it with 17-hydroxyprogesterone levels (17OHP) and corticoid dose at 10 years of age and at puberty onset.

Methods
Selection of children with CAH diagnosed from 1983/08/01 to 1995/08/01, followed in an outpatient clinic of paediatric endocrinology, with all necessary data in their clinical files: height, weight, 17OHP and corticoid dose at 10 years of age.

Conclusions
Because GH level is high at puberty compared to the level seen in adulthood data obtained in the oral glucose tolerance test in adulthood can not be extrapolated for children and adolescents. It is necessary to establish new cutoff for GH suppression in oral glucose tolerance test according to sex and pubertal stage both for normal height and tall stature.

DOI: 10.1530/endoabs.32.P807
There were 19 children with CAH: 8 boys; 11 girls (13 were diagnosed in the first year of life). The final height SDS was $-2.07$ ($-4.01$ to $-0.55$). It was different from the familiar height SDS: $1.33$ ($-2.34$ to $-0.22$; $P=0.003$). At puberty onset, their final SDS was $0.33$ ($-2.6$ to $5.14$); at 10 years of age, their height SDS was $0.29$ ($-1.69$ to $3.09$). The final height SDS had no statistically significant correlation with 17OHP and corticoid dose used at puberty onset, at 10 years of age or at the last clinical evaluation. The difference between the final height SDS and the pubertal height SDS was positively correlated with corticoid dose used at puberty onset ($r=0.466$; $P=0.044$); that difference was negatively correlated with 17OHP at puberty onset ($r=-0.643$; $P=0.004$).

Conclusion

In this group of children the final height SDS was inferior to the familiar, because of the poor growth after puberty onset. There wasn't any correlation with 17OHP and corticoid dose used during treatment.

DOI: 10.1530/endoabs.32.P807

P808
Sex steroid priming in differential diagnosis between idiopathic GH deficiency and constitutional delay of growth and puberty
Raffaella Radin1, Mirella Moro1, Massimo Scacchi1, Francesco Cavagni1, Leila Danesi1 & Luca Persani1,2
1Division of Endocrinology, Ospedale San Luca, Istituto Auzxologico Italiano IRCCS, Milan, Italy; 2Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy.

Primig with sex steroids prior to stimulation tests for the diagnosis of GH deficiency (GHD) in pubertal years remains controversial, though some evidence suggests its utility in improving the specificity of GH testing for the distinction between idiopathic GHD (IGHD) and constitutional delay of growth and puberty (CDGP). However, few data are available on the final height (FH) of untreated CDGP patients. In order to better understand the usefulness of priming, we analyzed the FH reached by two groups of consecutive IGHG or CDGP patients.

Study

Forty-five short children (30 males and 15 females; age 8, 9–16 years) underwent sex steroid priming (i.m. testosterone 100 mg; 1–2 mg oral estradiol) before GH stimulation test and were diagnosed with IGHG (25 patients) or CDGP (20 patients) depending on the results of testing. Only IGHG patients were treated with rhGH (0.025–0.035 mg/kg daily). All patients were followed-up until FH.

Results

Mean GH peak following testing was significantly lower in IGHG than in CDGP ($P<0.0001$). Mean IGF1 SDS was also significantly lower in IGHG ($P<0.01$); in particular, all children with IGFI SDS $<2.4$ (24% of total) were diagnosed with IGHG. Mean initial height SDS (IHSDS) was similar between the two groups, while target height SDS (THSDS) was significantly lower in IGHG ($P<0.05$). Both groups of patients reached a FH not statistically different from their TH.

Conclusions

i) Frankly low levels of IGF1 are highly suggestive of GHD, making the use of sex steroid priming unnecessary. ii) The significantly lower THSDS of IGHG patients suggests the contribution of inheritable factors in this category of children. iii) Our data support the usefulness of sex steroid priming in improving the ability of GH stimulation test to differentiate IGHG from CDGP, thus avoiding an unnecessary expensive treatment.

DOI: 10.1530/endoabs.32.P808

P809
Importance of gastroenterologist in successful recovery of anorexia nervosa patients
Marina Djurovic1, Dragan Popovic1,2, Dragana Jankovic1, Zvezdana Jemcovic1 & Milan Petakovic1
1Clinic for Gastroenterology, 11000 Belgrade, Serbia; 2Clinic for Gastroenterology, 11000 Belgrade, Serbia.

Presumption, nausea, bowel distension, abdominal pain and early satiety are very common in patients with Anorexia nervosa (AN). These problems may give rise to significant medical complications and may contribute to increased difficulties with refeding and weight restoration. The aim of our study was to evaluate the influence of gastrointestinal treatment on weight gain in AN patients. Esophagogastroduodenoscopy with gastric mucose biopsy were performed in 19 AN patients (DSM-IV criteria) with digestive problems (mean age 22.4 ± 0.7 years, BMI 15.9 ± 2.3 kg/m²) Pathohistological finding confirmed chronic gastric lesions in all AN patients and in ten patients Helicobacter pylori (HP) infection was found. The same examination was performed in 19 aged matched controls (25.2 ± 0.7 years, BMI 19.8 ± 0.4 kg/m²). No significant difference was found between HP positive and negative AN patients at the beginning of gastrointestinal treatment in BMI (15.86 ± 1.4 vs 16.1 ± 1.7 kg/m², $P>0.05$), as well as in serum leptin levels (1.69 ± 0.56 vs 2.38 ± 2.1 ng/ml, $P>0.05$). However, significant differences in BMI and serum leptin levels in AN vs controls(BMI 15.98 ± 1.3 vs 19.8 ± 0.4 kg/m², $P<0.01$; leptin 2.48 ± 0.5 vs 9.1 ± 1.6 ng/ml, $P<0.01$) were found. All AN patients were on hypernutrition and gastrointestinal therapy. After 6 months, in AN patients, significant difference in BMI and serum leptin concentrations (BMI 15.98 ± 1.3 vs 18.0 ± 1.3 kg/m², $P<0.001$; leptin 2.48 ± 0.5 vs 4.9 ± 0.7 ng/ml, $P<0.001$) were found.

Conclusion

Knowledge and treatment of gastrointestinal complications may be of critical importance in successful nutritive recovery in AN patients.

DOI: 10.1530/endoabs.32.P809

P810
Primary amenorrhea aetiologies: results from a monocenter study
Assila Lylia Amirou, Said Azzoug & Farida Chentli
Department of Endocrine and Metabolic Diseases, Bab Oued Hospital, Algiers, Algeria.

Introduction

Compared to secondary amenorrhea, primary amenorrhea is deemed to be a rare condition. Our aim is to study its annual frequency during a long period of time, and to analyze its different aetiologies in an Endocrine Department.

Methods

All patients referred for primary amenorrhea between 1980 and 2012 were studied. We took in account personal and family history, clinical examination, hormonal, cytogenetic and immunological assessments, and radiological explorations.

Results

155 cases were collected in 32 years = 4.8 case/year. Their mean age at diagnosis was 20.4 years. For different aetiologies, we found endocrine origin in 151cases = 97.5% and gynaecological causes in four patients (2.5%). The last ones were related to Rokitanski Kuster syndrome.

Among endocrine aetiologies, hypothalamic and pituitary causes were observed in 84 = 55.7%, ovarian causes in 54 = 35.7%, and male pseudo hermaphrodisisms in 13 = 8.6%.

Conclusion

In our study it appears that primary amenorrhea is a relatively rare consultation motive. The consultation was late in all cases. Gynaecological causes are rare. Among endocrine causes, hypothalamic and pituitary causes are prevailing. For ovarian causes, chromosomal causes are the most frequent. Male pseudo hermaphrodisisms account for 8.6%.

DOI: 10.1530/endoabs.32.P810

P811
Serum levels of 25(OH)-vitamin D and adipokine’s profile in obese children and adolescents
Andra Caragharcheorgopoul, Juliana Gherlan, Suzana Vladoiu, Florin Alexiu, Adriana Padure & Sorina Schipor
National Institute of Endocrinology ‘C.I.Parchon’, Bucharest, Romania.

Background

Low-serum concentrations of 25(OH)-vitamin D are associated with insulin resistance in adults. Recent in vitro studies have suggested that vitamin D may play a role in the regulation of adiponectin, leptin and resistin; since all these adipokines are related to insulin sensitivity modulation, they might represent a link between vitamin D status and insulin resistance.

Endocrine Abstracts (2013) Vol 32
Aim
To identify possible correlations between 25(OH)-vitamin D serum levels and adipokine’s profile in obese children and adolescents.

Material and method
Serum 25(OH)-vitamin D levels were assessed in 46 obese children and adolescents (age 14.3±2.2 years) compared to a control group of 30 age-matched healthy non-obese children (immunochemiluminescence). We measured in both groups fasting insulinnemia, HOMA-index, plasmatic levels of adiponectin, leptin and resistin.

Results
85.5% of subjects were vitamin D deficient (serum vitamin D <30 ng/ml; 87% in the obese group, 83.3% in the control group). The plasmatic levels of 25(OH)-vitamin D were not different between groups. The adiponectin levels were significantly lower and the leptin and resistin levels were significantly higher in the obese group compared to the control group. 25(OH)-vitamin D was negatively correlated to fasting insulinnemia (r=-0.324, P=0.036) and to plasmatic levels of leptin (r=-0.363, P=0.013); in multivariate regression analysis the only parameter that influenced vitamin D status in obese children was leptin.

We found no correlation between plasmatic levels of 25(OH)-vitamin D and the plasmatic levels of adiponectin or resistin.

Conclusion
We found a deficit of vitamin D in a large majority of selected Romanian children. Vitamin D deficit in obese children is related to hyperinsulinnemia, their association being explained by a parallel variation with plasmatic levels of leptin.

DOI: 10.1530/endoabs.32.P811

P812
Hepatic function in Berardinelli–Seip patients
Maria Fatima Baracho, Adriana Nunes, Maria Goretii Santos, Giovani Santos, Jhonatan Ferreira, Joao Aquino & Joao Brandao Neto
Federal University of Rio Grande do Norte, Natal, Rio Grande do Norte, Brazil.

Metabolic liver dysfunction can be a causative factor for morbity and mortality in Berardinelli–Seip syndrome patients. We evaluated hepatic function in 29 Berardinelli–Seip patients. Diabetes mellitus (DM) was present in 23 of them. We analyzed biochemical parameters including AST, ALT, GGT, ALP levels and liver non invasive imaging aspects. The liver was graded as normal, mild, moderate, or severe hepatic steatosis.

Results
We could not find significant correlation of DM diagnosis and dysfunction hepatic and steatosis. However we observed that time of diagnosis in these Berardinelli–Seip individuals showed relation to degrees of steatosis (P=0.004). It seems that the duration of clinical disease is more important than DM diagnosis regarding steatosis severity in these individuals.

DOI: 10.1530/endoabs.32.P812

P813
An adolescent girl with hypothyroid coma due to autoimmune thyroiditis
Ashraf Soliman, Noora Alhumaidi, Mayam Alali & Aml Sabt
Hamad Medical Center, Doha, Qatar.

Profound hypothyroidism leading to coma has not been reported in adolescents.

Case presentation
A 13-year-old adolescent girl presented with coma. Mother reported fatigue, increased sleepiness, deterioration of school performance, apathy, secondary amenorrea, change in voice, and weight gain for 5 months. No history of dyspnea, palpitations or chest pain, drug intake, trauma, or any systemic illness. No family history of endocrine disorders was reported. Mother reported that the girl lost consciousness after 30 min of feeling dizzy. She had hypothermia (36 °C), hypotension (BP=90/55 mmHg), and bradycardia (50/min). She was comatose (GCS=8/15) with periorbital edema, loss of the lateral eyebrows, dry skin, and large smooth symmetrical firm (40 g) goiter. Her TSH=417 mU/l and FT4 of 1.7 pmol/l (normal 11–19 pmol/l) and antimicosomal antibody (AMA) titer of 1:1800 confirmed the presence of severe hypothyroidism due to autoimmune thyroiditis. Thyroid ultrasonography revealed bilaterally enlarged thyroid lobes with heterogeneous echopattern and multiple nodules. MRI of the sella turcica revealed global diffuse enlargement of the pituitary. She received intravenous T3 therapy that regained her consciousness in 10 h, followed by intake of l-thyroxine 100 μg daily. Vigor returned and voice improved within 2 weeks. FT3 and TSH were normalized in 4 weeks. Pituitary size was normalized in the follow up MRI after 6 months.

Discussion
In this case presentation of hypothyroid coma is preceded by lethargy, depression, weakness, forgetfulness, cold intolerance and menstrual disturbance of insidious onset that was overlooked for 5 months. The presence of goiter, periorbital and facial edema and absence of lateral eyebrows were prominent. Aggressive therapy with intravenous thyroxine and external warming lead to excellent prognosis.

Conclusion
This case raises the awareness of physicians to include hypothyroid in the differential diagnosis of coma in this age group.

DOI: 10.1530/endoabs.32.P813

P814
Features of hyperprolactinemia syndrome in children
Olga Zagrebaeva & Anzhalka Solntsava
Belarusian State Medical University, Minsk, Belarus.

Aim
Evaluate the data of anamnesis, clinical-laboratory parameters, magnetic resonance imaging (MRI) findings, response to treatment in children with hyperprolactinemia (HProlact).

Methods
We analyzed retrospectively 16 patients in the endocrinological department of University hospital (Minsk) with HProlact over 2004–2012 years. Boys (B) 6 (37.5%) (stage on Tanner 1 – 1 (17%); stage 2–3 – 3 (50%), stage 4 – 2 (33%), age at diagnosis 11.4–15.9 years; girls (G) 10 (62.5%) (stage on Tanner 1–3 (30%), stage 2–3 – 2 (20%), stage 4 – 5 (50%), age at diagnosis 0.8–16.4 years. We examined BMI; the levels of prolactin, thyroid-stimulating hormone (TSH), free thyroxine; MRI. The results were processed using the Statistica 6.1.

Results
In anamnesis B: breast increasing 4 (66%), delayed puberty 1 (17%); G: precocious thelarche 3 (30%), dismenorrhoea 2 (20%), galactorrhoea 1 (10%), delayed puberty 1 (10%), headache 1 (10%). Prolactin B 49.8±3.9, G 48.9±4.2 (3–27.7 ng/ml) (P=0.6). Subclinical hypothyroidism was in 2 (33%) B and 4 (40%) G with TSH levels 6.4±1.8 and 5.7±1.1 (0.23–3.4 μU/l) (P=0.2). The remaining B and G were euthyroid. MRI confirmed the presence of microadenoma in 4 (66%) B and 5 (50%) G. G 4 (66%) B and 4 (57.2%) G received treatment with bromocriptine (1.25–2.5 mg/day). 3 (42.8%) G were treated with cabergoline (500 μg/week). Normal prolactin levels were noted in all B after 8.7±3.0 month of treatment. G which received bromocriptine normal prolactin were after 3±1.7 month, cabergoline – 4±2 (P=0.1). Tumor decreasing from 5 till 3 mm by MRI were in all B and G after 9.6±2.5 months and 4.7±2.5 respectively.

Conclusions
HProlact syndrome is rare in children. All cured patients with HProlact demonstrated a good response to medical treatment by normalization of prolactin values and decreasing of tumor.

DOI: 10.1530/endoabs.32.P814
P815

Growth disorders in Greece: baseline data from a multicentre observational study (GENESIS)

Kyrıakos Aloumanis1, Feneli Karachalios2, Elpis Vlachopapadopoulou2, Stephanos Michalacou3, Asteroula Papathanasiou2, Dionysis Chrysis4, Lela Stanoyannou2, Christos Kari2, Bessie Spilioti2, Vangelis Drossinos3 & George Chrousos3

1European Medical Research Institute by Pharmasure-Lilly, Athens, Greece; 23 A Kyriakou1 Athens Children’s Hospital, Athens, Greece; 3Agia Sofia2 Athens Children's Hospital, Athens, Greece; 4Patras University Hospital, Patras, Greece; 5 NKia General Hospital, Athens, Greece.

Aim
The Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS) is an open-label multinational observational study which collects information on management, clinical outcomes and treatment safety of children with growth disorders. Here we present descriptive data from the Greek cohort.

Methods and results
In Greece, 211 children (44.5% females, 136 naive to GH treatment at study entry and 18 not GH-treated) have been enrolled, after providing informed consent, in eight investigational sites, over 6 years (2005–2011).

GH deficiency (GHD, N 177) and Turner syndrome (TS) (N 20) were the main diagnoses upon enrolment. GHD was diagnosed with higher frequency in males than females (63.5 vs 36.5%). In patients where pubertal stage had been recorded, 70.4% of patients with GHD and 63.5% of patients with TS respectively. Baseline characteristics to be depicted in table.

Conclusions
In the Greek cohort of GeNeSIS, GHD is the most frequent cause for GH treatment, followed by TS. While the latter is diagnosed earlier, bone age to chronological age gap is numerically smaller and a higher GH initiation dose is administered. The results should be interpreted in the context of an observational, ongoing study.

DOI: 10.1530/endoabs.32.P815

P817

Williams syndrome: report of a case

Diana Coles1, Raluca Teleaunu2, Magdalena Sandu2 & Margarita Matei3

1National Institute of Endocrinology C.I. Parhon, Bucharest, Romania; 2Department of Pediatric Endocrinology, Victor Gomoiu' Clinical Children’s Hospital, Bucharest, Romania; Department of Endocrinology, Victor Gomoiu’ Clinical Children’s Hospital, Bucharest, Romania.

Introduction
Williams–Beuren syndrome is a rare genetic condition with clinical manifestations that include a distinct facial appearance, cardiovascular anomalies that may be present at birth or may develop later in life, idiopathic hypercalcemia, and a characteristic neurodevelopmental and behavioral profile.

Case report
We present a particular case of a 3.5 years old boy, born SGA at 39 weeks of gestation with neonatal hypoxia, diagnosed at 1.6 years old with Williams syndrome (FISH analysis: microdeletion 7q11.23 (ELN/D7S613-), after multiple neuropsychiatric evaluations for developmental delay and cognitive deficits.

Clinical exam
Normal stature, ponderal hypotrophy, facial dysmorphism: bilateral epicanthal folds, hypertelorism, microcephaly, short upturned nose, long philtrum, wide mouth, full lips, dental malocclusion and widely spaced teeth, micrognathia, blue–green eyes, stellate irises, lacrimal ducts imperforation; sunken chest, normotensive, systolic murmur, retracted testes, congenital fimosis, G1P1 Tanner stage; mild-moderate psychomotor delay, lower limb spastic hypertonia, hyperreflexia. Psychological examination: hyperkinetic, with mild heteroaggressive elements, attention deficit disorder, easily distracted; borderline intelligence.

Diagnosis
Echocardiography: mild supravalvar aortic stenosis, isolated septal hypoplasia. Normal renal function and ultrasound. Normal thyroid function, upper normal limit serum calcium (10.1 mg/dl, NV = 8.6–10.4 mg/dl), normal glycaemia.

Conclusion
Although the patient did not develop any endocrine feature by the time of presentation we report this case to illustrate a complex multisystem medical condition that requires a multidisciplinary team depending on the specific phenotype manifestations. Rehabilitation programs and educational interventions improve the prognosis and the social adjustment of the patient. This case needs family support and periodically referrals to pediatric neurologist and psychiatrist, cardiologist and/or cardiac surgeon, endocrinologist (for calcium and vitamin D levels, thyroid function, glucose tolerance testing, gonadal function), genitourinary tract ultrasound, assessments for visual problems or hearing loss.

DOI: 10.1530/endoabs.32.P817

P816

Predicting growth response among Egyptian idiopathic isolated GH deficient children

Nermin Salah1,2, Soha Abd El Dayem1,2, Lobna Fawaz1,2 & Marwa Ibrahim1,2

1Faculty of medicine, Cairo University, Cairo, Egypt; 2Pediatrics Department, National Research Centre, Cairo, Egypt.

Objective
To determine the Predictors of growth response to GH treatment in a group of isolated idiopathic GH (GH).

Patients and methods
477 GH deficient (GHD) children with GH therapy were included in the study. Patients were followed up for a minimum of 1 year up to 6 years. Multiple linear regressions were done to identify predictors of growth response to rGh in the first 4 years of treatment.

Results
In the first year, three significant predictors of growth were identified: GH peak (ln (m/mg)), age of onset of therapy and target height-height SDS. In the 2nd and 3rd years of therapy, GV was both significantly and positively correlated to the GV (cm/year) of the previous year.

Conclusion
We conclude that, prediction models offer a valuable tool for individualization and assuring adherence to GH and thus a cost effective treatment, which is the ultimate goal of GH therapy.

DOI: 10.1530/endoabs.32.P816

P818

Case report: two patients with Di George syndrome with different diagnostic peculiarities

Diana Coles1, Raluca Teleaunu2, Daniela Vasile2 & Margarita Matei3

1National Institute of Endocrinology C.I. Parhon, Bucharest, Romania; 2Department of Pediatric Neurology, ‘Victor Gomoiu’ Clinical Children’s Hospital, Bucharest, Romania; Department of Endocrinology, ‘Victor Gomoiu’ Clinical Children’s Hospital, Bucharest, Romania.

Introduction
Di George syndrome is a genetic disorder caused by deletion of chromosome 22. The main features are congenital heart defects, absence or hypoplasia of thymus (with consecutive immunodeficiency and infections), hypoparathyroidism with hypocalcaemia, gastrointestinal problems, delayed psychomotor development, craniofacial abnormalities, tendency to develop seizures and psychiatric disorders.

Case report
We present the case of two patients with different peculiarities regarding age at diagnosis, clinical features that arose suspicion and lead to genetic testing. First case: a 13.6 years old boy is diagnosed with Di George syndrome in FISH analysis after presenting for over 1 year muscle cramps in lower limbs and constipation due to hypocalcaemia, multiple respiratory tract infections, mild facial dysmorphism (considered familial and did not raise any suspicion until now), scoliosis, seizures, attention deficit hyperactivity disorder. Laboratory tests: hypoparathyroidism – hypocalcaemia, euthyroidism, negative for autoimmune thyroid disorder, normal serum cortisol and ACTH; normal CBC. No thymus evaluation or immunologic tests yet available. Normal renal and cardiac ultrasound.

DOI: 10.1530/endoabs.32.P818
Second case an 6-year-old girl with genetic confirmation of 22q11.2 microdeletion at 4 years old. Clinical presentation: normal stature, overweight (+3.34 s.d.), mild craniofacial dysmorphism: long face, tubular nose, mild hypoplasia of nasal wings, low-set ears posterior rotation, hypernasal voice. She was diagnosed with epilepsy at 11 months. Psychological evaluation: delay in expressive language and psychosomatic development, polymorphic dislalia. Laboratory tests: normal calcium, euthyroidism. Normal renal ultrasound.

Conclusion
Common aspects for both patients are euthyroidism, developmental delay and learning difficulties, low performance intelligence quotient, absence of thymus disorders but recurrent infections in both patients' medical history require further immunology tests to be assessed. Both are children with special needs requiring continual care and supervision (because of metal retardation, seizures, neurological and psychiatric disorders).

DOI: 10.1530/endoabs.32.P818

P819
Egyptian GH deficient patients: demographic, auxologixcal characterization and response to GH therapy
Nermia Salah1, Soha Abd El Dayem2, Fatma El Mogy3, Lobna Fawaz1 & Marwa Ibrahim1
1Pediatrics Department, Faculty of medicine, Cairo University, Cairo, Egypt; 2Pediatrics Department, National Research Centre, Cairo, Egypt; 3Clinical Pathology Department, Faculty of medicine, Cairo University, Cairo, Egypt.

Objective
To study the growth response to GH treatment in GH deficient patients. Also to report the possible side effects emerging during treatment with GH.

Patients and methods
477 GH deficient (GHD) children were included in the study. All patients received biosynthetic GH therapy at a dose of 20 IU/m² per week. Patients were followed up for a minimum of 1 year and up to 6 years as anthropometric assessment was performed every 3 months, while thyroid profile was followed every 6 months. Student’s t-test was used for analysis of two quantitative variables.

Results
Patients with complete GHD and multiple pituitary hormone deficiency (MPHD) were significantly shorter as expressed in their height SDS, target height-height (SDS) and a more bone age delay (P<0.05). Patients with complete GH showed better growth response compared to those with partial GHD in the first 2 years of therapy.

Conclusion
We conclude that anthropometric assessment is the corner stone in GHD diagnosis and follow up, where catch up growth occurs in the first 2 years of therapy followed by a plateau. GH therapy is generally safe.

DOI: 10.1530/endoabs.32.P819

P820
Male pseudo hermaphroditism due to the association of two very rare conditions: a deficit in 17β-hydroxysteroid dehydrogenase type 3, and a chimera
Saida Kabour, Said Azzoug & Farida Chentli
Department of Endocrine and Metabolic Diseases, Bab Oued Hospital, Algiers, Algeria.

Introduction
In medical practice ambiguous genitalia is a relatively rare condition. The combination of two causes in genital malformation is exceptional. Our aim is to describe a person having an abnormal karyotype with a chimeraism (46,XY/46,XX) and a deficit in 17β-hydroxysteroid dehydrogenase 3 (17β-HSD): an enzyme in the testes that transforms D4 Androsterone to testosterone and androstenedione to dihydro testosterone or DHT. Case report
X aged 21, whose parents are cousins, educated as a girl, came for primary amenorrhea. Clinical examination showed deep voice, mild ambiguous genitalia, chloro-megalay and two testes (one in the scrotum and the second highly situated). The breast was Tanner’s stage 1, body hair pattern looks like a woman’s. Hormonal evaluation showed high testosterone for a woman and low for a man (9.25 nmol/l) and very high D4A (13 ng/ml). On ultrasound female structures were absent. Pelvis MRI confirmed both testes and seminal vescicles. The karyotype showed a mosaic: 46,XY (96%) and 46,XX (5%) or chimeraism.

Conclusion
In our case, the male pseudo hermaphroditism is apparently due to the combination of two exceptional abnormalities. The first one is a chimera in which the person has the male chromosomal complement (XY), but some cells have the female chromosomal complement (XX). The second is also a very rare as partial deficit in 17β-HSD3, i.e. enzyme that transforms D4A to testosterone and androsterone to DHT. Both exceptional situations can lead to ambiguous genitalia.

DOI: 10.1530/endoabs.32.P820

P821
Results of investigation of children and adolescents (boys) with different disorders of puberty development in Bukhara city and four districts (Republic of Uzbekistan)
Utukr Mavlonov1 & Yulduz Urmanova1,2
1Bukhara State Medical Institute, Bukhara, Uzbekistan, 2Tashkent Pediatic Medical Institute, Bogishamol 223, Tashkent, 100140, Uzbekistan.

Aim
To find and study character of clinical disorders of children and adolescents (boys) with different disorders of puberty development.

Materials and methods
During April–May 2012 we examined 521 children and adolescents (boys) in Bukhara city and four Bukhara districts schools. 143 of them were underwent general clinical examination as well as biochemical and hormonal investigations (levels of LH, FSH, GH, testosterone, sex-steroid ass. globulin, prolactin, cortisol, TSH, T4, T3, etc.), roentgenologic examination (Turkish saddle CT and MRI and hand roentgenogram), clinical ultrasound of the thyroid and sex organs, anthropometric examination, having their sexual development stage by Tanner assessed. Mean age of boys was from 11.0 to 16 years.

Results
Examination of 521 boys allowed diagnosing a number of different disorders of puberty development in 143 boys (29.4%). By character of pathology the examinees were divided into three groups. The 1st group included 106 patients from 143 (74.1%) with delay of puberty, the 2nd group including 13 patients (9.09%) with retardation of puberty and growth, the 3rd group including 11 patients (7.7%) with gynecomastia (one of boys having obesity), the 4th group – five patients (3.5%) having micropenis+obesity, the 5th group – two patients (1.4%) having varicocele, the 6th group – 2 patients (1.4%) with anorchia, the 7th group – two patients (1.4%) having cryptorchidism, the 8th group – and one patient (0.6%) having precocious puberty.

Conclusions
i) Among disorders of puberty development in teenagers more frequent found delay of puberty (74.1%). ii) There are different disorders of puberty development was established: retardation of puberty and growth (9.0%), gynecomastia (7.7%), micropenis obesity (3%), varicocele (1.4%), cryptorchidism (1.4), and precocious puberty (0.6%).

DOI: 10.1530/endoabs.32.P821

P822
Hormonal results of investigation of adolescents (boys) with delay of puberty
Yulduz Urmanova1,2, Utukr Mavlonov1,2 & Alla Abdurakhmanova1,2
1Tashkent Paediatric Medical Institute, Bogishamol 223, Tashkent, 100140, Uzbekistan; 2Bukhara State Medical Institute, Bukhara, Uzbekistan.

Aim
To study hormonal results of investigation of adolescents (boys) with delay of puberty.

Materials and methods
We choose 32 teenagers from 106 boys with symptoms of delay of puberty development in the age of 15 years old. They were underwent general clinical examination as well as biochemical and hormonal investigations (levels of LH, FSH, GH, testosterone, prolactin, cortisol, TSH, T4, radio-immunological lab of The Center of Endocrinology, PhD, Abdurakhmanova A.M.).

Results
The hormonal investigation of 32 boys allowed diagnosing a number of different disorders. The mean level of LH was 2.8 mMIE/l (5.1 ± 0.6), FSH – 3.4 mMIE/l (6.1 ± 4.9), TSH – 1.82 mMIE/l, total testosterone – 8.9 ng/ml (mean 6.24 ng/ml), prolactin – 7.4 nmol/l (5.8), cortisol – 289.25 nmol/l (250–720), and T4 – 17.4 ng/ml.

Endocrine Abstracts (2013) Vol 32
Conclusions
i) The hormonal investigation of teenagers with mean age 15 years old submitted, that most of our patients (29 from 32) had hypogonadotropic hypogonadism (90.6%) and ii) only one patient had hypergonadotropic hypogonadism (3.1%).
DOI: 10.1530/endoabs.32.P822

P823
Gene expression profiling of familial and sporadic pituitary adenomas
Sayka Barry1, Emanuela Gaddaleti1,2, Claude Chelala1,2 & Marta Korbonits1
1Barts and the London School of Medicine, William Harvey Research Institute, Centre for Endocrinology, Queen Mary University of London, John Vane Science Centre, Charterhouse Square, London EC1M 6BQ, UK; 2Molecular Oncology, Barts Cancer Institute, Queen Mary University of London, 1st Floor, John Vane Science Centre, Charterhouse Square, London EC1M 6BQ, UK.

Background
Familial isolated pituitary adenoma (FIPA) is recently identified autosomal dominant condition with incomplete penetrance. Heterozygote mutations have been identified in the aryl-hydrocarbon receptor interacting protein (AIP) gene in 20–30% of FIPA families. AIP mutation positive patients have distinct phenotype: the disease is occurring at a younger age and have more aggressive tumours.

Aims
The aim of this study was to perform comparative gene expression analysis of AIP positive, AIP negative and sporadic tumours to discover the genes/pathways responsible for the AIP positive phenotype and to understand the underlying molecular mechanisms involved in the pituitary tumorigenesis.

Methods
We have performed gene expression analysis on normal pituitary, sporadic GH-secreting adenomas, AIP positive and AIP negative familial somatotroph adenomas (five samples of each category) using the Affymetrix human Gene Chip HG-U133 Plus 2.0 array. Data analysis was carried out in the statistical R environment. Ingenuity pathway analysis (IPA) tool was used for pathway analysis. Expression of the five selected genes from microarray analysis was validated by quantitative reverse transcriptase PCR.

Results
We have identified a large number of differentially expressed genes in pituitary adenomas compared to normal pituitary. In addition, a small number of genes differ in their expression levels between familial AIP positive and sporadic adenomas. These genes are involved in epithelial-to-mesenchymal transition (EMT), extra-cellular matrix (ECM) remodelling and cellular invasion. qRT-PCR data of the increased expression of mesenchymal marker, invasive markers and the decreased expression of epithelial markers were consistent with the microarray data.

Conclusion
These results indicate that these transcriptional changes likely reflect the clinically seen more aggressive phenotype in AIP positive patients. In pituitary tumorigenesis EMT likely occurs within a specific genetic context and may be related to their increased local invasion and more aggressive behaviour. Therefore, different pathways in pituitary adenoma progression exist.
DOI: 10.1530/endoabs.32.P823

P824
Role of filamin-A in the regulation of SSTR2 receptor localization and signalling in tumoral GH-secreting cells
Elena Giardino1, Erika Peverelli1, Eleonora Vitali1, Valeria Cambiaghi1,2, Anna Spada1 & Marta Korbonits1
1Endocrine Unit, Department of Clinical Sciences and Community Health, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy; 2Endocrine Unit, IRCCS Humanitas Clinical Institute, Rozzano, Italy.

Somatostatin (SS) binds to different SS receptors (SSTR1–5) and SS analogues are the first choice medical treatment of GH-secreting pituitary adenomas (GH-omas). A subset of patients is resistant to SS, although the mechanisms involved in SS resistance are not fully understood. Recent studies identified specific protein–protein interactions as determinant in the regulation of receptor anchoring and signalling. Filamin A (FLNA) is a widely expressed cytoskeleton protein that, through its scaffolding properties, affects the intracellular signalling and trafficking of a number of receptors. Based on our recently published data, FLNA is crucial for D2 receptor expression and signalling in lactotrophs. Since SSTR2 was recently found to associate with FLNA, the aim of this study was to investigate the role of FLNA in SSTR2 signalling and targeting in human GH-omas and GH3, a rat pituitary GH-secreting cell line. We studied FLNA expression in GH-omas (n = 10) by western blotting (WB) and its role in GH3 by gene silencing technique. Confocal microscopy was used to evaluate receptor SSTR2 localization and WB to evaluated cyclin CD1 and SSTR2 expression.

In all GH-omas FLNA was expressed at variable levels, without any significant correlation with the clinical phenotype. In GH3 cells FLNA gene silencing did not induce changes in SSTR2 total levels. Similarly, this manipulation did not affect receptor localization at the plasma membrane. On the contrary, the reduction in cyclin D1 levels induced by the selective SSTR2 agonist (Bim23120) in GH3 was abolished in FLNA silenced cells. These data suggest that FLNA might be implicated in intracellular signalling of SSTR2 by mediating at least some of its antiproliferative effects. In contrast, FLNA does not appear to be necessary for receptor expression and localization at the plasma membrane.
DOI: 10.1530/endoabs.32.P824

P825
Drosophila melanogaster as a model organism to study aryl hydrocarbon receptor interacting protein gene function
Elena Daniela Allorei1, Chenghao Chen1, Benjamin Klapholz3, Ashley B Grossman2, Nicolas Tapón2, Nicholas H Brown1, Ralf Stanewsky2 & Marta Korbonits1
1Department of Endocrinology, Barts and the London School of Medicine, Queen Mary University of London, London, UK; 2School of Biological and Chemical Sciences, Queen Mary, University of London, London, UK; 3Department of Physiology, Development and Neuroscience, The Gurdon Institute, University of Cambridge, Cambridge, UK; 4Department of Clinical Oncology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, University of Oxford, Oxford, UK; 5Aptosis and Proliferation Control Laboratory, Cancer Research UK, London Research Institute, London, UK.

Introduction
Loss-of-function mutations in AIP are associated with familial isolated pituitary adenoma, often leading to gigantism due to invasive GH-secreting pituitary adenomas. One challenging problem in the management of patients carrying a missense AIP variant is to determine whether the missense variant is a disease-causing mutation or not. As most of the molecular mechanisms involved in the control of growth and the cell cycle are well-conserved, we propose to utilise the fruitfly to determine putative disease-causing human variants. The Drosophila melanogaster AIP orthologue gene CG1847 codes for a protein with a similar size and structure.

Methods
We created CG1847 deficiency either via RNAi knockdown (using two different RNAi-lines) or via knockout with the help of imprecise excision of a P-element located inside the 5'-UTR of CG1847 gene.

Results
When a universal driver (actin) was used to express the CG1847 RNAi, no viable adult offspring were observed, indicating that complete AIP knockdown is lethal. To confirm these results with a different approach, we generated imprecise excisions of a P-element and deletion of a 1497 bp fragment, creating a loss-of-function mutation of Drosophila AIP (CG1847exon1,2). This mutant is lethal in males (females are viable being heterozygotes for this CG1847exon1,2 mutation).

Conclusion
We have demonstrated that total deficiency of CG1847 leads to lethality in fruitfly similar to results in AIP-KO mice, confirming that CG1847 is an essential gene for fly development. In our future experiments we will attempt to rescue the fruitfly CG1847exon1,2 mutant with human AIP, and then we will make mutants containing different human AIP missense variants. These experiments should ultimately test the degree of functional conservation between fly and human, and help to determine whether the missense variant is likely to be a disease-causing mutation or not.
DOI: 10.1530/endoabs.32.P825
**P826**
The role of GLI1 in pituitary tumor formation and pituitary cell survival

Katharina Lampichler1, Patrizio Fererer1, Greisa Vila1, Anton Luger1, Engilbert Knosp1, Ludwig Wagner1 & Sabina Baumgartner-Parzer2
1Division of Endocrinology and Metabolism, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria; 2Division of Neurosurgery, Department of Surgery, Medical University of Vienna, Vienna, Austria; 3Division of Nephrology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria.

The transcription factor and proto-oncogene GLI1 is the terminal mediator of the Hedgehog signalling pathway which is involved in developmental processes, stem cell maintenance and cell proliferation. Although the pathway is mainly active during embryogenesis and tissue repair, it is frequently reactivated in several cancer types.

Based on these findings we investigated the potential role of GLI1 in the pathogenesis of pituitary adenomas. GLI1 expression was studied in 30 human pituitary adenomas by qRT-PCR. Additionally, mRNA expression levels of stem cell marker SOX2, cell cycle regulator TP53, proliferation marker Ki67 and superoxide dismutase (SOD) 1 were determined. The threshold of GLI1 expression was set to be 1% of the GAPDH copy number level. Furthermore, the murine pituitary adenoma cell line A1T-20 was treated with the GLI1 antagonist GANT61 and cell viability was evaluated. 19 out of 30 human pituitary adenomas (63%) showed a GLI1 overexpression of various extent. GLI1 expression correlated with the expression of SOX2 (P < 0.001, r = 0.5813), TP53 (P < 0.001, r = 0.6111), Ki67 (P = 0.0385, r = 0.5889) and SOD1 (P < 0.001, r = 0.5889). Expression levels of all the above mentioned genes exhibited also a significant correlation among each other, creating a network of cell cycle regulators and stem cell factors potentially involved in the pathogenesis of pituitary adenomas. Of note, survival rates of A1T-20 cells were highly decreased when treated with GLI1 antagonist GANT61. Cell survival was reduced by 50% (24 h) and 75% (48 h), respectively, upon treatment with GLI1 antagonist GANT61. Additionally, the death rate increased further at a concentration of 20 μM of GANT61 and could be further decreased at a concentration of 20 μM resulting in complete cell death after 48 h.

In conclusion, our results suggest that GLI1 is potentially involved in the pathogenesis of pituitary adenomas by modulating adult stem cell fate or tumor-initiating stem cell function in the adult pituitary gland and its neoplasms.

DOI: 10.1530/endoabs.32.P826

---

**P827**
cAMP exerts proliferative and anti-proliferative effects in pituitary cells of different types by activating both cAMP-dependent protein kinase A and exchange proteins directly activated by cAMP

Eleonora Vitali1, Gika Peverelli1, Giovanna Mantovani1, Elena Giardino1, Andrea G. Lania2, Paolo Beck-Peccoz1 & Anna Spada1
1Endocrine Unit, Department of Clinical Sciences and Community Health, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy; 2Endocrine Unit, IRCCS Humanitas Clinical Institute, Rozzano, Italy.

cAMP is implicated in the inhibition or stimulation of proliferation depending on cell type. The activation of cAMP-PKA pathway generates proliferative signals in GH-secreting adenomas whereas this effect is not present, or even opposite, in non-functioning pituitary cells (NFPA). Although cAMP effects were initially attributed to PKA activation, recently the discovery of two cAMP-activated guanine nucleotide exchange factors (Epac1,2) was proposed as a novel mechanism for governing signalling specificity within the cAMP cascade. The aim of the present study was to investigate the effects of cAMP in different pituitary cell types on cell proliferation and to determine the specific role of PKA and Epac in mediating these effects.

We tested the effects of different cAMP analogs (PKA-selective, Epac-selective or non-selective) on cell proliferation, evaluating also the expression of cyclin D1/D3 and the cyclin dependent kinase inhibitor p27, in different pituitary adenomas (GH, PRL-secreting or non secreting adenomas) and in appropriate cell lines (GH3, MMQ and HP75).

We found that non-selective cAMP analog caused a 50% stimulation of somatotroph cells proliferation, whereas they exerted an opposite inhibitory effect on lactotrophs (~55%) and non-functioning (~58%) pituitary cells, these data being obtained also in the corresponding cell lines and confirmed by the expression of CD1, CD3, p27 proteins. Moreover, stimulatory and inhibitory effects induced by cAMP analog were mimicked by the PKA- and Epac-selective cAMP analogs.

In conclusion, we demonstrated that cAMP exerted opposite effects on proliferation in different pituitary cell types and that these effects are mediated by both PKA and Epac through the activation of different pathways, i.e. CREB and Rap1 respectively.

DOI: 10.1530/endoabs.32.P827

---

**P828**
Expression of somatostatin receptors, SSTR2A and SSTR5, in 108 pituitary adenomas, using immunohistochemical detection with specific MABs

Laura Chinezu1, Alexandre Vasiljevic1,2, Emmanuel Jouanneau1,3, Patrick Francois1, Angela Bordi1, Gerald Ravetot1 & Jacqueline Trouillas1,2
1Department of Histology, University of Medicine and Pharmacy Targu Mures, Targu Mures, Romania; 2Université Lyon 1, Université de Lyon, INSERM, UMR-S1028, Lyon Neuroscience Research Center, Oncocfam Team, Lyon, France; 3Hospices Civils de Lyon, Lyon, France; 2Service de Neurochirurgie, Hôpital Bretonneau, Centre Hospitalier Régional Universitaire de Tours, Tours, France.

Background
Medical treatment of pituitary adenomas with somatostatin analogs depends on tumor type and somatostatin receptor expression. Using polyclonal antibodies, their immunohistochemical (IHC) detection gave conflicting results. Therefore, we studied the IHC expression of SSTR2A and SSTR5 using two specific MABs in five types of pituitary adenomas.

Methods
SSTR2A and SSTR5 expression was studied using two MABs (clone UMB1 and UMB4 for type 2A and 5 respectively) in 108 pituitary adenomas classified into five types: GH (n = 60), ACTH (n = 15), FSH/LH (n = 23), PRL (n = 7) and TSH (n = 3). A comparative study was performed using two IHCs (Bouin-Holland and Formalin-Zinc) and two technical procedures (manual and automated IHC).

Results
Expression of SSTR2A and SSTR5 was classified as positive (more than 10% of immunoreactive cells) or negative (less than 10% of immunoreactive cells) in five types of adenomas.

Conclusion
SSTR2A and SSTR5 were only highly expressed in GH and TSH adenomas. The IHC detection of SSTR with MABs is a reproducible and specific method which can be performed in everyday practice and could be helpful to predict post-operative treatment with somatostatin analogs, in particular in ACTH adenomas.

DOI: 10.1530/endoabs.32.P828

---

**P829**
miR-146 mediated IGF1 proliferative effects on a rat pituitary GH/PRL secreting pituitary adenoma cell line

Mariaenrica Bellino1, Cecilia Mirabassi2, Teresa Gagliano1, Ettoredegli Uberti1 & Maria Chiara Zatelli1,2
1Section of Endocrinology, University of Ferrara, Ferrara, Italy; 2Laboratorio in rete del Tecnopolo ‘Tecnologie delle terapie avanzate’ (LTTA) of the University of Ferrara, Ferrara, Italy.

IGF1 represents an important growth factor in pituitary physiology and pathology, also mediating the positive feed-back mechanisms on somatotroph axis. It has been previously demonstrated that IGF1 promotes cell viability in primary cultures of human non functioning pituitary adenomas, by mechanisms involving, at least in part, mTOR signaling, which is involved in many pathways controlling cell proliferation. We aimed at investigating whether mTOR may mediate IGF1 effects also in an in vitro model of GH/PRL secreting pituitary adenoma, the rat GH3 cells. Therefore, GH3 cells were incubated in the presence or in the...
absence of 100 nM IGFI with either Everolimus, an mTOR inhibitor, or NVP-BEZ235, a PI3K/mTOR inhibitor at concentrations ranging from 10 to 500 nM for 72 h. We found that the lowest Everolimus concentration that significantly inhibited cell viability was 25 nM, with a cell viability reduction of 50% (P < 0.01). The lowest NVP-BEZ235 concentration that significantly inhibits cell viability is 50 nM, with a cell viability reduction of 40% (P < 0.01). In addition, IGFI significantly increased cell viability by 20–60% at concentrations ranging from 10 to 500 nM, independently of the concentration. These proliferative effects were completely abrogated by co-incubation with 50–100 nM Everolimus or NVP-BEZ235. On the other hand, 50–100 nM Everolimus or NVP-BEZ235 significantly promoted caspase 3/7 activity (15–25%; P < 0.02). Basal apoptotic rate was not significantly influenced by IGFI, which did not protect GH3 cells from proapoptotic effects of Everolimus and of NVP-BEZ235. These results confirm that IGFI has proliferative effects on pituitary adenoma cells, which are mediated, at least in part by mTOR. On the contrary, IGFI does not prevent the pro-apoptotic effects of mTOR inhibitors.

DOE: 10.1530/endobs.32.P829

P830

Mutations of SOX2 gene: a novel heterozygous mutation and impact on congenital hypopituitarism

Renata S Auriemma1,2, Annamaria Macchiarioli3, Daniel Kelberman4, Maria F Faienza5, Rosalia Corona1, Iolanda Marianno1, Sara Giangiobbe5, Mariano Galdiero5, Rosario Pivonello5, Annamaria Colo5 & Maurizio Gaspert1

Section of Endocrinology, Department of Medicine and Health Sciences, University of Molise, Campobasso, Italy; 2Section of Endocrinology, Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy; 3Paediatric Endocrinology Unit, ‘Cardarelli’ Hospital, Campobasso, Italy; 4Developmental Biology Unit, UCL Institute of Child Health, London, UK; 5Department of Medicine, University ‘Aldo Moro’, Bari, Italy.

Introduction

Anophthalmia/microphthalmia is a rare developmental craniofacial defect often associated with congenital hypopituitarism with GH deficiency and hypogonadism. SOX2 gene plays a key role in embryonic development regulation and heterozygous mutations of this gene, reported only in 14 patients to date, have been associated to anophthalmia/microphthalmia and congenital hypopituitarism in up to 10% of cases. Therefore, the study of the SOX2 gene can be clinically useful in determining etiology and appropriate therapeutic approaches.

Patient and methods

We report the case of a novel SOX2 gene mutation in a 17 years old male patient with congenital anophthalmia and hypopituitarism. Brain magnetic resonance imaging (MRI) showed complete agenesis of corpus callosum and occular bulbs with optic nerve hypoplasia, whereas hormonal assays revealed GH deficiency and hypogonadism. Start of hypogonadism requiring the appropriate replacement therapy. Familial investigation did not show the same phenotype in any of first-degree relatives. The coding region of the SOX2 gene was sequenced.

Results

The novel heterozygous SOX2 inactivating mutation c.905delC, predicting the frameshift p.Pro302Arg fs*69, was found. Genetic counseling was recommended in all first-degree relatives. The coding region of the SOX2 gene was sequenced.

Conclusions

This case illustrates the importance of genetic testing of SOX2 gene to aid correct diagnosis and to assist in clinical management.

DOE: 10.1530/endobs.32.P830

P831

Characterization of somatostatin receptor expression in MENX-associated pituitary adenomas: impact on therapy and imaging with somatostatin analogs

Miss Lee1, Amelie Lupp2, Florian Gärtner3, Justo P Cañaza4, Stephan Schuelz5 & Natalia Pellegrata6,7

1Institute of Pathology, Helmholtz Zentrum München, Munich, Germany; 2Institute of Pharmacology and Toxicology, University of Jena, Jena, Germany; 3Department of Nuclear Medicine, Klinikum rechts der Isar, Technische Universität München, Munich, Germany; 4Department of Cell Biology, Physiology and Immunology, University of Córdoba, Cordoba, Spain; 5Institute of Pathology, University of Bern, Bern, Switzerland.

Introduction

Somatostatin analogs (SSAs) are the first-line clinical treatment for patients with pituitary adenomas (PAs) but their efficacy is highly variable among patients. This could be due to a differential expression of somatostatin receptor subtypes (Ssrs) among tumors, but this issue is still unresolved. Nonfunctioning pituitary adenomas (NFPA)s, which mostly derive from gonadotroph cells, are among the tumors that poorly respond to SSAs. Rats carrying a germline loss-of-function mutation in p27 (MENX syndrome) develop gonadotroph adenomas that closely resemble human gonadotroph tumors. To determine whether rat PAs can be used to explore the relationship between Ssr expression and response to SSA, we determined the expression profile of Ssrs in these tumors and assessed their response in vitro to the SSA octreotide.

Methods

Adenoma tissues or primary PA cells from MENX-affected rats were used. qRT-PCR, immunohistochemistry (IHC) and in vitro autoradiography were performed to determine Ssrs expression. Rat primary PA cells were treated with the octreotide and cell viability assessed. Small animal positron emission tomography (PET) was performed using the somatostatin agonist 68Ga-DOTA-NOC.

Results

We observed higher expression of Ssrt2 and Ssrt3 mRNA in PA cells from mutant rats when compared with cells from wild-type rats. Accordingly, Ssrt2 protein was found more highly expressed in the rat tumors (especially the small ones) than in non-tumorous pituitary areas by IHC. Ssrt3 protein was also detectable in the rat tumors. Treatment of rat primary PA cells in vitro with octreotide showed that they partially respond to the drug, similarly to human NFPA. By 68Ga-DOTA-NOC-PET imaging, we found the increased uptake in the pituitaries of mutant rats in vivo when compared with wild-type rats.

Conclusion

Studies of MENX-associated PAs might help us understand the relationship between Ssr expression and response to SSAs in NFPA.

DOE: 10.1530/endobs.32.P831

P832

Clinical and morphological characteristics of dopamine agonist-resistant prolactinomas

Natalia Fedorova1, Larisa Dzeranova1, Ekaterina Pigarova2, Alexander Abdrosimov1, Liudmila Astaf’eva1 & Liudmila Rozhinskaya1

Endocrinology Research Centre, Moscow, Russia; 2Burdenko Neurosurgery Institute, Moscow, Russia.

Introduction

The aim of our study was to investigate clinical and morphological features of dopamine agonist-resistant prolactinomas.

Methods/design

The study included 51 patients (38 women, 13 men) with prolactin-secreting pituitary adenoma that is resistant to treatment with dopamine agonists, age 15–82 years.

Results

Median of the serum PRL level distribution at the onset of the disease was 4500 mU/l (3480, 140 300). The MRI showed nine patients (17.6%) had microadroma, 42 patients (82.4%) – macroadroma, in 14.3% of the cases a giant adenoma was found. 31 patients underwent surgery (60.8%), and six patients were operated repeatedly. Radical surgical treatment, estimated as reaching normoprolactinemia and no residual adenomatous tissue, was seen in 35.5% of the cases (11 patients). In addition, five patients (16.1%) the surgery resulted in medical control of hyperprolactinemia with lower doses of cabergoline than those before the surgery. 20 adenoma samples were investigated by immunohistochemistry. In the study of the expression of PRL, the diagnosis of prolactinoma was confirmed in 19 patients (95%), one patient did not reveal any expression of tropic hormones. Co-expression of the GH was found in seven patients (36.8% of the 19 patients with PRL immunopositivity), although clinical acromegaly was not observed in these patients, with normal values of IGF1. The MRI showed that 35.5% of the cases (11 patients). In addition, five patients (16.1%) the surgery resulted in medical control of hyperprolactinemia with lower doses of cabergoline than those before the surgery. 20 adenoma samples were investigated by immunohistochemistry. In the study of the expression of PRL, the diagnosis of prolactinoma was confirmed in 19 patients (95%), one patient did not reveal any expression of tropic hormones. Co-expression of the GH was found in seven patients (36.8% of the 19 patients with PRL immunopositivity), although clinical acromegaly was not observed in these patients, with normal values of IGF1. The expression of TSH, ACTH, LH, FSH was not found in any case. The expression of dopamine receptor type 2 was confirmed in 13 cases (65%). The presence of somatostatin receptor expression type 2 (SSR2) was detected in five patients (25%), SSR3 – in eight patients (40%), SSR2 and SSR3 – in three patients. Estrogen receptor expression was detected only in one case (5%). None of the patients showed expression of progesterone receptors.

Conclusion

Resistance to treatment with dopamine agonists is a serious problem; more often patients with resistant prolactinomas have macroadromas. Surgical treatment is effective in 35.5% of cases. We can assume that resistance to treatment with dopamine agonists is associated with low expression of dopamine receptors in the
cells of removed adenomas. Low expression of SSRI2 and SSR5 in these patients may indicate the failure of therapy with somatostatin analogues. Thus, further study and search for effective treatments for these patients are required.

DOI: 10.1530/endoabs.32.P832

P833

Expression of connexins 26, 32 and 43 mRNA in normal and pituitary adenomas
Bruno Nunes1,2, Manuel dos Santos Faria2, Rodrigo Fortunato1, Luiz Eurico Nasciutti3, Ulrich Renner1, Günter K. Stall3, Denise Pires de Carvalho1 & Leandro Miranda-Alves1
1Universidade Federal do Rio de Janeiro, Rio de Janeiro/RJ, Brazil; 2Institute of Psychiatry, Munich, Germany.

Connexins are a proteins critically involved in the formation of gap junction, which connect cells with each other and enable the exchange of small compounds and, besides having a role independently of gap junction formation. At least, in the anterior pituitary two cellular networks have already been identified, one of them is composed of the endocrine inactive folliculo-stellate cells and the second one is the GH-producing somatotroph cell network. It is supposed that gap junctions may play an important role in these networks. The network organization of endocrine and non-endocrine cells of the anterior pituitary may be of high functional relevance and may allow a more rapid and coordinated release of hormones and/ or growth factors. Loss of these network structures during non-functional relevance and may allow a more rapid and coordinated release of hormones and/ or growth factors. Therefore, we examined the expression of connexins 26, 32 and 43 in normal pituitary and endocrine-inactive adenomas, somatotropinomas and corticotropinomas. We determined mRNA expression using real time reverse transcriptase PCR (qRT-PCR) in series of pituitary tumors. Our initial results demonstrated a decrease in connexins expression in most of adenomas studied. We observed a decrease in expression of connexin 26 in 12 tumors of 14 non-functioning adenomas, in six tumors of seven corticotropinomas and in four tumors of four somatotropinomas when compared it with normal pituitary connexin 26, 32 and 43 expression. We analyzed connexin 32 mRNA expression in these adenomas the data showed that a decrease in connexin expression in ten adenomas of 13 non-functioning adenomas, in five adenomas of five corticotropinomas and in five adenomas of five somatotropinomas. Finally, we also observed a decrease in connexin 43 mRNA expression in 12 adenomas of 14 non-functioning adenomas, in three adenomas of five corticotropinomas and in five adenomas of five somatotropinomas. Taken together, these data raise questions about the possibility of connexins are participating in the tumorigenesis and/or the pathophysiology of pituitary adenomas.

DOI: 10.1530/endoabs.32.P833

P834

No correlation between somatostatin 2 receptor expression analyzed by RNA in-situ hybridization and real-time qRT-PCR in clinically non-functioning pituitary adenomas
Filip Gabalec1, Aleš Kohout1, Jan Laco2, Monika Drastikov2, Martin Beranek1, David Netuka1, VACLAV MASOPUST4, Tomas Cesak5 & Jan Cap1
14th Department of Internal Medicine, Faculty of Medicine in Hradec Králové, Charles University Hospital, Hradec Králové, Czech Republic; 2Fingerland’s Department of Pathology, Faculty of Medicine in Hradec Králové, Charles University Hospital, Hradec Králové, Czech Republic; 3Faculty of Medicine in Hradec Králové, Institute of Clinical Biochemistry and Diagnostics, Charles University Hospital, Hradec Králové, Czech Republic; 4Department of Neurosurgery, 1st Faculty of Medicine, Central Military Hospital, Charles University, Prague, Czech Republic; 5Department of Neurosurgery, Faculty of Medicine in Hradec Králové, Charles University Hospital, Hradec Králové, Czech Republic.

Objective
The aim of this study was to quantitatively estimate SSTR2 in clinically non-functioning pituitary adenomas (CNFAs) with use of RNA in-situ hybridization (ISH) and quantitative real-time RT-PCR and correlate the results of both methods.

Methods
A standard histological and immunohistochemical examination was performed on the resected pituitary tumour. Afterwards in-situ hybridization for somatostatin 2 receptor (SSTR2) RNA was performed manually using the RNAscope® 2.0 FFPE Assay (Advanced Cell Diagnostics, Inc., Hayward, CA, USA) on formalin fixed and paraffin embedded tissue sections. Small part of the same tumour resected during operation and stored in RNAlater was used for quantitative real-time RT-PCR.

Results
A 25 adenomas with SSTR2 mRNA expression in qRT-PCR were chosen for further evaluation with RNA ISH. SSTR2 mRNA was expressed in all adenomas from 1413–1486 copies/μl cDNA; the median of relative quantity (after normalization to housekeeping gene GUS) for SSTR2 was 111%. In contrast to qRT-PCR immunostaining was positive only in nine adenomas with the use of RNA ISH. Positive cases were subsequently semi-quantitatively assessed according to the manufacturer’s scoring guideline as follows: 1 adenoma with 1 +, 5 with 2 + and 3 with 3 +. No adenoma scored 4 + although high expression of SSTR2 mRNA was present. We did not find any correlation between data ( Spearman’s rank correlation coefficient 0.243).

Conclusion
Use of somatostatine analogues or dopastatins remains controversial in CNFAs. Verification of SSTR presence before use of drug treatment should be useful. Both RNA ISH and qRT-PCR have their pitfalls. In our case, we did show no correlation between these methods. RNA ISH is definitely less sensitive and specific. We think that interpretation of results for SSTR2 expression in RNA ISH and qRT-PCR should be very careful.

Project is supported by Ministry of Health Project No. NT/11344-4/2010.

DOI: 10.1530/endoabs.32.P834

P835

FSH and LH cells in normal-fed male rats after centrally applied ghrelin
Verica Milosevic1, Vladimir Ajdzanovic1, Dejan Nestic2, Vesna Starcevic2, Natasa Ristic3, Rasko Rakovic3 & Darko Stevanovic3
1Institute for Biological Research 'Sinisa Stankovic', University of Belgrade, Belgrade, Serbia; 2School of Medicine, Institute of Medical Physiology, University of Belgrade, Belgrade, Serbia.

Ghrelin, the endogenous ligand of GH secretagogue receptor type 1a, has emerged as a pleiotropic modulator of diverse biological functions, including energy homeostasis and recently, reproduction. The effects of i.c.v. administered ghrelin on morphological characteristics of pituitary FSH- and LH-cells were examined in adult male Wistar rats. The animals were randomized in two groups: control and experimental group, each consisted of seven animals, and implanted with an i.c.v. cannula. After a recovery period, experimental males received 1 μg ghrelin/μl PBS during 5 days, while control males received the same volume of saline vehicle. Experimental and control males were sacrificed under ether narcosis 2 h after the last injection. FSH- and LH-producing cells were studied using the peroxidase-antiperoxidase (PAP) immunohistochemical procedure. The FSH and LH cells of adult control males were polygonal, oval or polyhedral in shape with prominent, often eccentrically located nuclei. They were strongly immunostained and positioned throughout the pituitary pars distalis, alone or in groups, often in close contact with blood capillaries. After i.c.v. treatment with ghrelin, FSH and LH cells in the pituitaries were smaller in size, less intensely immunostained and their shape was irregular comparing to the controls.

In animals i.c.v. treated with ghrelin volume of FSH cells and volume of their nuclei were significantly decreased (P < 0.05) by 34.0 and 37.1% respectively, while the parameters of LH cells were unchanged when compared to the control values. The volume density of LH cells in animals i.c.v. treated with ghrelin was significantly decreased (P < 0.05) by 38.9%, but the volume density of FSH cells was not altered in comparison with the controls. In conclusion, our results indicate that i.c.v. applied ghrelin have inhibitory effect on the volume of FSH cell and volume of their nuclei, as well as on relative volume density of LH cells.

DOI: 10.1530/endoabs.32.P835
**P836**

**PTTG and Ki-67 expression in pituitary adenomas**

Filip Golkowski1, Grzegorz Sokolowski1, Iga Wierzbicka-Tutka2, Agata Balsys-Waligorska1, Dariusz Adamek1 & Alicja Hubalewska-Dydejczyk1

1Department of Endocrinology, Jagiellonian University Medical College, Kraków, Poland; 2Department of Gastroenterology, Hepatology and Infectious Diseases, Jagiellonian University Medical College, Kraków, Poland. 

**Material and methods**

The Ki-67 and PTTG indices were determined by immunohistochemistry in specimens excised from neurosurgically removed pituitary tumours. In fifty two examined patients (30 females and 22 males, mean age 50.5 ± 15.4 years) who underwent pituitary tumour surgery, micro- and macroadenoma occurred in 10 and 42 cases respectively.

**Results**

The expression of Ki-67 and PTTG were revealed only in cells of pituitary adenomas respectively. The median values of Ki-67 and PTTG indices were 1.56% (IQR 3.05) and 1.02% (IQR 2.27) respectively. The index of PTTG, contrary to Ki-67 index, was significantly higher in adenomas with positive anterior pituitary hormone expression (n = 40) as compared with adenomas with negative anterior pituitary hormone expression (n = 12) (1.22 (IQR 2.17) vs 0.12 (IQR 1.07), P < 0.05). Both Ki-67 and PTTG indices were not significantly related to tumour size category (microadenoma/macroadenoma) and were not correlated with tumour size. Contrary to Ki-67, PTTG index was significantly correlated with patient age (r = −0.267, P = 0.026). We found no correlation of both above-mentioned indices with expression of pituitary hormones in examined specimens.

**Conclusion**

Expression of Ki-67 and PTTG was observed in the majority of pituitary adenomas. Ki-67 and PTTG expression, as determined in pituitary tumour specimens, was not related to the tumour size and kind of pituitary hormone expression.

DOI: 10.1530/endoabs.32.P836

**P837**

**Medical therapy of acromegaly**

Ana Palha, Luisa Cortez, Teresa Sabino, José Silva Nunes, António Afonso, Fernando Fonseca & Ana Agapito

Centro Hospitalar Lisboa Central, Hospital Curry Cabral, Lisbon, Portugal.

**Introduction**

Medical therapy of acromegaly is indicated in patients who failed to achieve remission after surgery, with contraindication or refusal for surgical therapy or following radiotherapy in order to bridge the interval until complete remission.

**Objectives**

Evaluate the medical therapy – somatostatin analogs (SSAs), dopamine agonist (DAs) and GH receptor-antagonist (Pegvisomant) – in acromegalic patients followed from 1988–2011.

**Methods**

We conducted a retrospective study of 52 acromegalic patients (32 women) submitted to medical therapy. Criteria for disease control (normal age- and sex-adjusted IGF1 concentration and GH below 1 ng/ml) were evaluated by the average of three values. A reduction below 20% of those parameters after SSA was considered as an absence of response to this therapy.

**Results**

Medical treatment was the only option for eight patients, complemented surgery in 29, isolated radiotherapy in one, and radiotherapy combined with surgery in 14. SSA were used in 43 patients (seven experienced no response). A normal GH and IGF1 concentration was achieved in 16.2% of 36 patients, with an average IGF1 reduction of 54.2%.

**Conclusion**

In total, 26.5% (n = 13) of the patients were under control. Of those not controlled (n = 36), 30% displayed a dissociated response (IGF1 or GH) and 40.6% registered IGF1 levels only 10% above upper limit of normal.

**Around 25% of our patients were controlled. Half of patients not under control displayed a dissociated response. Adding DA to SSA doesn’t seem to improve the results.**

DOI: 10.1530/endoabs.32.P837

**P838**

**Daidzein affects the stereological parameters of pituitary GH cell in orchidectomized adult rat**

Svetlana Trifunovic, Vladimir Ajdzanovic, Branko Filipovic, Marko Miler, Natasa Ristic, Ivana Medigovic & Veronica Milosevic

Institute for Biological Research, Belgrade, Serbia.

**Daidzein, one of the main phytoestrogens of soy, is able to act as estrogen-like compounds due to its structural similarity with 17β-estradiol, which gives them the capacity to bind estrogen receptors and to induce hormone-like effects. Considering, that somatotropic system is sensitive to sex steroids, the aim of this study was to investigate the effects of daidzein on stereological and biochemical parameters of pituitary somatotropic (GH) cells in orchidectomized adult rat. Adult Wistar rat were divided into two groups: orchidectomized rat s.c. treated with medium (absolute etanol and sterile olive mixture; Orx) and orchidectomized rats s.c. treated with daidzein in medium (30 mg/kg BW; Orx + D). The groups of animals received the treatment during three weeks and were sacrificed 24 h after the last injected dose. Immunohistochemically labeled pituitary section were stereologically analysed, using NewCast Stereological Software Package. The circulating GH was determined biochemically. The volume density of pituitary GH cells was increase (P < 0.05) after daidzein treatment (25.6 ± 2.4%), in comparison to Orx group (20.1 ± 1.15%). In addition, intensity of staining of GH cell and volume of GH cells were increased (P < 0.05) after daidzein treatment (217.2 ± 110.8 μm3), in comparison with Orx group (1203.8 ± 174.9 μm3) as well. Numerical density and absolute number of GH cells were decrease (P < 0.05) after daidzein treatment (10.8 ± 0.6×104 mm−3; 5.6 ± 0.8×104 respectively), in comparison to Orx group (16.8 ± 2.1×104 mm−3; 7.6 ± 0.9×104). The treatment did not affect GH level in blood. These results indicated that daidzein has provoked different changes of the stereological parameters of GH cells, which did not affect GH blood level. It can be concluded that response of somatotropic system to daidzein treatment includes, beside regulation at the level of the pituitary gland, other mechanisms of regulation of GH secretion.**

DOI: 10.1530/endoabs.32.P838

**P839**

**8-Prenylnaringenin decreases hormone expression in GH3 pituitary adenoma cells of the rat**

Rosita Rupa1, Benjamin Voellger2, Elmar Kirches3, Christian Mawrin2 & Raimund Firsching1

1Klinik fuer Neurochirurgie, Otto-von-Guericke-Universitaet Magdeburg, Magdeburg, Germany; 2Institut fuer Neuropathologie, Otto-von-Guericke-Universitaet Magdeburg, Magdeburg, Germany.

**Objective**

8-Prenylnaringenin (8-PN) is a phytoestrogen discovered in hops. GH3 pituitary adenoma cells of the rat show a variety of responses to phytoestrogens in vitro. This in vitro study aims to analyze changes in hormone expression in GH3 cells treated with 8-PN.
Methods
GH3 cells were incubated with 0.5–50 μM 8-IPN for 4 h. Medium and ethanol served as controls. Changes in expression of growth hormone (GH) and prolactin (PRL) normalized to β2 microglobulin (β2MG) were assessed using quantitative real time PCR (QRT-PCR). T served as statistical test. P < 0.05 was supposed to be statistically significant.

Results
In GH3 cells treated with 0.5–50 μM 8-IPN, expression of GH and PRL is decreased as compared to controls. Significant differences in GH expression were found after treatment with 0.5 μM 8-IPN as compared to ethanol (P = 0.042), 0.5 μM 8-IPN as compared to medium (P = 0.011), 5 μM 8-IPN as compared to medium (P = 0.022) and 50 μM 8-IPN as compared to medium (P = 0.013). Significant differences in PRL expression were found after treatment with 0.5 μM as compared to ethanol (P = 0.039) and 50 μM 8-IPN as compared to ethanol (P = 0.046).

Conclusion
Further investigation of the impact of 8-IPN on hormone expression and secretion in GH3 cells is warranted.

DOI: 10.1530/endoa.32.P839

Pituitary – Clinical (Generously supported by IPSEN)

P840

Early and sustained tumour volume reduction and GH/IGF1 control in patients with GH-secreting pituitary macroadenoma primarily treated with lanreotide Autogel 120 mg for 48 weeks: the PRIMARYS study

Philippe Caron1, John Bevan2, Antoine Clermont3 & Pascal Maisonobe3

1Department of Endocrinology and Metabolic Diseases, CHU Larrey, Toulouse, France; 2Department of Endocrinology, Aberdeen Royal Infirmary, Aberdeen, UK; 3Ipsen Pharma, Boulogne-Billancourt, France.

Introduction
First-line somatostatin analogue treatment may be an effective alternative option to surgery for some patients with GH-secreting pituitary macroadenoma. The PRIMARYS study aimed to investigate the impact of primary lanreotide Autogel 120 mg treatment on tumour volume and GH/IGF1 control in treatment-naive acromegalic patients over a one-year time course.

Methods
PRIMARYS was an international, multicentre, open-label, single arm, phase 3b study (NCT00690898/EudraCT2007-000155-34). Treatment-naive acromegalic patients with GH-secreting pituitary macroadenoma demonstrated that primary treatment with lanreotide Autogel 120 mg every 28 days rapidly achieved tumour reduction of pituitary adenoma volume and sustained GH/IGF1 control. These data support further exploring the potential use of lanreotide as an initial therapeutic option in this patient population.

Conclusions
This large prospective study enrolling treatment-naive acromegalic patients with GH-secreting pituitary macroadenoma primarily treated with lanreotide Autogel 120 mg every 28 days daily achieved tumour reduction of pituitary adenoma volume and sustained GH/IGF1 control. These data support further exploring the potential use of lanreotide as an initial therapeutic option in this patient population.

DOI: 10.1530/endoa.32.P840

P841

The benefits of pasireotide in patients with Cushing’s disease are not restricted to patients with normalisation of UFC; results from a large, 12-month study

Rosario Pivonello1, Stephan Petersenn2, Feng Gu3, Andrew Trovato4, Gareth Hughes5, Monica Ligueros-Saylan5, Luíz Roberto Salgado6, André Lacrotte7, Jochen Schopohl8 & Beverly Biller9

1Federico II University, Naples, Italy; 2ENDOC Center for Endocrine Tumors, Hamburg, Germany; 3Peking Union Medical College Hospital, Beijing, China; 4Novartis Pharma AG, Basel, Switzerland; 5Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA; 6University of São Paulo Medical School, São Paulo, Brazil; 7Centre hospitalier de l’Université de Montréal, Montréal, Canada; 8University of Munich, Munich, Germany; 9Massachusetts General Hospital, Boston, Massachusetts, USA.

Introduction
Pasireotide normalized or reduced UFC in patients with Cushing’s disease in a large, 12-month study. This analysis evaluates the effects of pasireotide on the signs/symptoms of Cushing’s disease according to the degree of UFC control.

Methods
Adult patients (n = 162) with persistent/recurrent or de novo Cushing’s disease were randomized to pasireotide 600/900 μg s.c. bid. Dose titration (max: 1200 μg bid) was allowed after month 3 and initiation/change in antihypertensive, antidiabetic and lipid-lowering medications was permitted throughout the study. Changes in the symptoms of Cushing’s disease during pasireotide treatment were evaluated at 6 and 12 months. UFC measurements were conducted at central laboratories. UFC control was defined as UFC ≤ULN, partial control as UFC > ULN but with at least 50% reduction from baseline, and uncontrolled UFC as UFC > ULN without a ≥50% reduction from baseline.

Results
In general, improvements in blood pressure, weight and BMI were observed in patients with and without UFC control, although the greatest changes were observed in those with UFC control (see Table). Similar results were seen for facial rubor and striae. Fasting plasma glucose and HbA1c levels increased from baseline in all patients receiving pasireotide, irrespective of UFC control. The relative impact of concomitant medications on signs and symptoms could not be evaluated.

Endocrine Abstracts (2013) Vol 32
The results of sandostatin LAR therapy in acromegalic patients

Corina Galeasa1, Ilinca Groza1, Anda Loghin1, Alexandru Florescu1 & Danisia Haba2

1Department of Endocrinology, University of Medicine and Pharmacy ‘Gr. T. Popa’, Iasi, Romania; 2Department of Radiology, University of Medicine and Pharmacy ‘Gr. T. Popa’, Iasi, Romania.

Introduction
Somatostatin analogs, formerly used as adjuvants in acromegaly treatment, are widely used as primary treatment today.

Objective
To investigate the efficacy of octreotide therapy in acromegalic patients as primary or secondary therapy.

Materials and methods
Four acromegalic patients diagnosed at the Endocrinological Clinic (males, mean age 35–75 years, age range 26–49 years, all patients with macroaomadoma) were treated with octreotide. Among them, three patients received octreotide preoperatively and one postoperatively. The concentration of human GH (HGH) and IGF1 was evaluated at 0, 6 and 12 months, while magnetic resonance imaging (MRI) was taken before treatment and 12 months after. All patients received initially octreotide 20 mg/28 days. The dose was adjusted by the individual patient’s response. Mean treatment duration was 25–75 months (range 6–43 months).

Results
Mean serum GH fell from 53 ng/ml (range 51.7–130.6) to 13 ng/ml (range 2.03–29.83) at the 3 months visit and remained suppressed. Mean plasma IGF1 concentrations fell from 502.5 ng/ml (range 327–838) to 490.25 ng/ml (range 320–677) at three months. Patients with higher initial GH concentrations were less likely to normalize IGF1 concentrations during treatment. After 1 year of therapy, tumor size decreased with a mean value of 22.58% in 75% of cases. Dose increments above 30 mg/28 days at one patient did not provide additional benefit in terms of hormonal reduction. The symptoms were ameliorated in 75% of patients. The most common adverse events were gastrointestinal; one patient developed gallstones but was asymptomatic.

Conclusions
Octreotide treatment of acromegaly not only decreases GH and IGF1 concentrations, but also appears to diminish the size of the tumor.

DOI: 10.1530/endoabs.32.P843

P844
Spanish molecular registry of pituitary adenomas: a multicenter, translational approach aimed at improving patient management
Alfonso Leal-Cerro1, Raul M Luque2, Laura Sánchez-Tejada3, Alejandro Ibáñez-Costa4, Mireia Jordá3, María A Gálvez5, Miguel A Japón6, Esther Rivero-Cortés6, Ruth Sánchez-Ortiga7, Raquel Buj1, Eva Venegas1, Elena Dios1, Susan M Webb7, Alfonso Soto-Moreno1, Carmen Fajardo1, Ignacio Bernabé1, Pedro Benito-López1, Manel Puig-Domingo5, Antonio Picó1 & Justo P Castaño1
1Instituto de Biomedicina de Sevilla (IBIS), Consejo Superior de Investigaciones Científicas, Endocrinology Unit of Virgen del Rocío University Hospital, University of Seville, Seville, Spain; 2Department of Cell Biology, Physiology and Immunology of University of Córdoba, Reina Sofia University Hospital, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), CIBER Fisiopatología, Córdoba, Spain; 3Endocrinology and Nutrition Unit, Department of Clinical Medicine, Hospital Universitario de Alzarate, Universidad Miguel Hernández, Alicante, Spain; 4Institut de Medicina Predictiva i Personalitzada del Cancer (IMPPC), Barcelona, Spain; 5Service of Endocrinology and Nutrition, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), Reina Sofia University Hospital, Córdoba, Spain; 6Department of Pathology, Virgen del Rocío University Hospital, Sevilla, Spain; 7Endocrinology/Medicine Departments, Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBER-ER, Unidad 747), ISCIII, Hospital Sant Pau, Universitat Autònoma de Barcelona (UAB), Barcelona, Spain; 8Service of Endocrinology, Hospital de la Ribera, Alzira, Valencia, Spain; 9Endocrinology Department, Complejo Hospitalario Universitario de Santiago de Compostela (SERGAS), Fundación para una Investigación, Desarrollo e Innovación Ramón Domínguez (Fundación Ramón Domínguez), Santiago de Compostela, Spain.

Pituitary adenomas are heterogeneous, rare tumors, which hinders analysis of large numbers of cases with common approaches. To overcome this, a multicenter, clinical-based strategy was proposed aimed at enhancing the tools

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Change from baseline to month 6 (mean (95% CI))</th>
<th>Change from baseline to month 12 (mean (95% CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>C (n=32)</td>
<td>PC (n=22)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>C (n=32)</td>
<td>PC (n=22)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>C (n=32)</td>
<td>PC (n=22)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>C (n=32)</td>
<td>PC (n=22)</td>
</tr>
</tbody>
</table>

Conclusions
Reduction in UFC levels observed during treatment with pasireotide was accompanied by corresponding improvements in the signs and symptoms of Cushing’s disease, which were maintained for 12 months. Importantly, improvements were observed even without complete UFC normalization, suggesting that partial improvements in UFC produced by pasireotide may be beneficial in improving signs and symptoms in patients with Cushing’s disease.

DOI: 10.1530/endoabs.32.P844

P842
Exploration of hand size as a screening tool for acromegaly
Gudrun Hackenberg, Sylvère Störmann, Josefine Rommler, Sandra Rutz, Jochen Schoehl & Harald J Schneider
Medizinische Klinik und Poliklinik IV, Ludwig-Maximilians-Universität, Munich, Germany.

Introduction
There is a long delay between the onset of symptoms and correct diagnosis of acromegaly. This study aimed to explore the potential of hand size as a screening tool for acromegaly. This approach allows defining clinical cutoff levels with a high specificity. In men, hand diameters at the 95th percentile (representing a specificity of 95%) was 192.07 and 152.90 cm² and the hand diameter at the 95th percentile was 11.47 cm, P < 0.01 vs 8.87 cm, P = 0.001) reached same significance. In women, palm surface areas at the 95th percentile (representing a specificity of 95%) was 145.02 cm² and the hand diameter at the 95th percentile was 4.9 cm, P < 0.005) was 11.30 cm, P < 0.001) reached same significance.

Results
The results of this study were partially supported by Pfizer.

DOI: 10.1530/endoabs.32.P842

P843
The results of sandostatin LAR therapy in acromegalic patients

This study was partially supported by Pfizer.

DOI: 10.1530/endoabs.32.P843
to diagnose and manage pituitary tumors by combining clinical/pathological/molecular information. This initiative was developed by the Sociedad Andaluza de Endocrinología y Nutrición, and further endorsed by the Sociedad Española de Endocrinología y Nutrición, and supported by Novartis. A comprehensive strategy based on a coordinated network was designed covering all Spanish reference centers for pituitary pathology. To develop a shared database registering clinical, pathological and molecular information for each patient and minimize intercenter variability, common protocols and methods were set up for tissue collection, clinical and pathological and molecular data analysis and registry. This joint initiative, named Spanish molecular registry of pituitary adenomas (REMAH) was established in 2010 and organized in six regional nodes. A common database has been generated (http://www.remahnacional.com) including clinical and pathological information. A standardized system for adenoma molecular phenotyping was developed and validated. Specifically, 26 genes were evaluated by quantitative real-time PCR, including pituitary hormones, receptors for somatomedin, dopamine, GHHR, GnRH, CRL, vasopressin and ghrelin, plus additional selected markers (K-actin, HPRT, and GAPDH). Molecular information was obtained on 250 tumors, out of 634 patients registered until 2012. Initial analysis indicates a close parallelism of the molecular profile of the adenoma subtypes with previously reported data and with the clinical phenotype of the patients, and also provide additional information on specific receptors known as drug-targets. REMAH is a unique, country-wise, multi-centric, multi-disciplinary network of expertise supported on a shared database enabling a translational, more powerful approach to the management of pituitary adenomas, paving the way for innovative clinical-basic studies with large numbers of patients of these rare pathologies.

DOI: 10.1530/endoabs.32.P844

P845
Pasireotide LAR and octreotide LAR maintain inhibition of GH and IGF1 in patients with acromegaly: 12-month extension phase of a randomized, double-blind, multicenter, phase III study

Michael Sheppard1, Marcello Bronstein2, Pamela Freda3, Omar Serri4, Laura De Marinis5, Luciana Naves6, Liudmila Rozhinskaya7, Karina Hernosillo Reséndiz8, Matthieu Ruffin9, Kobby Asubonteng8 & Gunter K. Stalla10, Vyacheslav Pronin11, Dominique Matter12,1, Jerome Berherat12, Annamaria Colao13,1, Irena Illovskaia14, Diego Ferone15, Margaret Zacharin16, Roberto Salvatori17 & Albert Beckers18

1University of Birmingham, Edgbaston, Birmingham, UK; 2University of Sao Paulo Medical School, Sao Paulo, Brazil; 3Columbia University College of Physicians and Surgeons, New York, New York, USA; 4University of Montreal, Montreal, Canada; 5Università Cattolica del Sacro Cuore, Rome, Italy; 6University of Brasilia, Brasilia, Brazil; 7National Research Center for Endocrinology of the Russian Academy of Medical Science, Moscow, Russia; 8Novartis Pharmaceuticals Corporation, Florham Park, New Jersey, USA; 9Novartis Pharma AG, Basel, Switzerland; 10Università Federico II di Napoli, Naples, Italy.

Introduction
Pasireotide LAR was significantly superior to octreotide LAR at providing biochemical control in a 12-month trial in 358 medially naive patients with acromegaly. Patients with clinical benefits of GH < 2.5 μg/l and IGF1 ≤ ULN could continue therapy in the extension study.

Methods
Patients entering the extension (pasireotide LAR, n = 74; octreotide LAR, n = 46) were followed up to month 26 (core plus extension) for octreotide LAR, whereas pasireotide LAR patients could continue beyond month 26. Dose titration to pasireotide LAR 60 mg/28 days or octreotide LAR 30 mg/28 days (if GH ≥ 2.5 μg/l and/or IGF1 > ULN) or to pasireotide LAR 20 mg/28 days or octreotide LAR 10 mg/28 days (for tolerability) was permitted throughout core and extension.

Results
Mean duration of exposure was 465 days (pasireotide LAR) and 412 days (octreotide LAR). 51 pasireotide LAR and 36 octreotide LAR patients completed month 26. Suppression of GH and IGF1 was maintained throughout the extension in both arms. Median GH (μg/l) and IGF1 (×ULN) in pasireotide LAR vs octreotide LAR patients were: at baseline, 8.8 vs 10.1 and 2.9 vs 2.9; at month 12, 1.5 vs 2.0 and 0.9 vs 1.3; and at month 25, 1.0 vs 1.0 and 0.6 vs 0.9. Median percentage change in GH and IGF1 at month 25 was −83% and −71% with pasireotide LAR and −86% and −64% with octreotide LAR. Mean percentage change in tumor volume from core baseline to month 25 was −51.8% (n = 54) for pasireotide LAR and −55.0% (n = 34) for octreotide LAR. Both treatments improved acromegaly symptoms scores. Most common AEs during the core and extension in both treatment arms were diarrhea, cholelithiasis, hyperglycemia, headache, and diabetes mellitus. Hyperglycemia-related AEs were more frequent with pasireotide LAR than octreotide LAR (62.9% (n = 112/178) vs 25.0% (n = 45/180)).

Conclusions
These results suggest that pasireotide LAR and octreotide LAR provide long-term inhibition of GH and IGF1 in patients with acromegaly.

DOI: 10.1530/endoabs.32.P845

P846
Characteristics of patients with pituitary gigantism: results of an international study

Liliya Rostomyan1, Adrian F. Daly1, Maria Tichomirowa1, Luciana A. Naves2, Nalini Shah3, Philippe Chanson4, Sabina Zacharieva5, Constantine A Stratsis6, Sebastian Neggers7, Ian Holaday8, Gunter K. Stalla9, Vyacheslav Pronin10, Dominique Matter11,1, Jerome Berherat12, Annamaria Colao13, Irena Illovskaia14, Diego Ferone15, Margaret Zacharin16, Roberto Salvatori17 & Albert Beckers18

1Department of Endocrinology, University of Birmingham, Edgbaston, Birmingham, UK; 2University of Sao Paulo Medical School, Sao Paulo, Brazil; 3Novartis Pharmaceuticals Corporation, Florham Park, New Jersey, USA; 4Novartis Pharma AG, Basel, Switzerland; 5Università Federico II di Napoli, Naples, Italy.

Aim
To analyse a large series of patients with pituitary gigantism.

Materials and methods
We included in this multicentre study 158 patients (129 males) with pituitary adenoma (PA) or hyperplasia and current/previous abnormal, excessively rapid growth velocity for age or a final height greater than 2 SD above normal for their population. Data of patients were systematically recorded in case report forms. Results
The first symptoms developed at median age of 15 years (11–19). 96% had facial changes and/or acral overgrowth at time of diagnosis. Age at diagnosis: PA in females were younger than in males (16.5 vs 23 years) with median delay in diagnosis of PA of 5 years. Twenty-four patients were still growing and had median height of 191 cm (171–199). One hundred and thirty-four patients had stopped growing at age of 20 years (18–22). The relative difference from calculated midparental height was significantly greater in those with control of GH-excess after 20 years old than before (10.9% (8.4–15) vs 7.9% (5.9–10.3), P = 0.012). Most PA were macroadenomas (84%), with median maximal tumour size of 25 mm (14.5–37). More than 50% of cases had extrasellar extension (77%) or invasion (54%). 4% had pituitary hyperplasia. One hundred and forty-five patients were operated with remission after first operation in 14% and in 0% in those who were reoperated (26 patients). Multimodal treatment approach was in 40% and disease control was achieved in 43% (median follow up on treatment was 7 years (2–16)). Hypopituitarism increased in frequency from 24% at
P847
Switching patients with acromegaly from octreotide LAR to pasireotide LAR improves biochemical control; crossover extension to a randomised, double-blind, multicenter, Phase III study

Pamela Freda1, Maria Flesseriu2, Aart Jan van der Lely3, Annamaria Colao4, Michael Sheppard5, Feng Gu6, Chiung-Chyi Shen7,8, Monica Gadela9, Andrew Farrall10, Karina Hermosillo Reséndiz11, Matthieu Ruffin12, YinMiao Chen13 & Marcello Bronstein13

1Columbia University College of Physicians & Surgeons, New York, New York, USA; 2Oregon Health & Science University, Portland, Oregon, USA; 3Erasmus University Medical Centre, Rotterdam, The Netherlands; 4Universita’ Federico II di Napoli, Naples, Italy; 5University of Birmingham, Edgbaston, Birmingham, UK; 6Peking Union Medical College Hospital, Beijing, China; 7Tri-Service General Hospital and National Defense Medical Center, Taipei, Taiwan; 8Hungkang University, Taichung, Taiwan; 9Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil; 10University of Edinburgh, Edinburgh, UK; 11Novartis Pharmaceuticals Corporation, Florham Park, New Jersey, USA; 12Novartis Pharma AG, Basel, Switzerland; 13University of São Paulo Medical School, São Paulo, Brazil.

Introduction
In a Phase III trial, pasireotide LAR was significantly superior (P = 0.007) to octreotide LAR at providing biochemical control at 12 months in medically naive acromegaly patients (post-pituitary surgery or de novo). Inadequately controlled patients (GH ≥ 2.5 mg/l and/or IGF-1 > ULN) at the end of core study were eligible for switching therapy (crossover extension). Reported here are efficacy results up to 12 months and safety results up to 15 months post-crossover.

Methods
Eligible patients were switched to either pasireotide LAR 40 mg/28 days (n = 81) or octreotide LAR 20 mg/28 days (n = 81). One dose escalation to pasireotide LAR 60 mg/28 days or octreotide LAR 30 mg/28 days was permitted, but not mandatory, post-crossover. Main outcome measures included GH < 2.5 µg/l and normal IGF-1 12 months after switching medical therapy.

Results
A 31 pasireotide LAR and 13 octreotide LAR patients discontinued within 12 months after crossover. Response rates (95% CI): 12 months after crossover to pasireotide LAR (n = 81) and octreotide LAR (n = 81; respectively): GH < 2.5 µg/l and normal IGF-1, 17.3% (9.8–27.3) and 0%; normal IGF-1, 27.2% (17.9–38.2) and 5.3% (0.6–17.7); GH < 2.5 µg/l, 44.4% (33.4–55.9) and 23.7% (11.4–40.2); tumor volume decreased from extension baseline by a mean (SD) of 20.0% (25.2) and 17.9% (27.8). A significant (≤ 20%) tumor volume reduction from extension baseline was seen in 54.3% (25/46) of pasireotide LAR and 42.3% (11/26) of octreotide LAR patients. Safety profile of both agents was consistent from extension baseline was seen in 54.3% (25/46) of pasireotide LAR and 42.3% (11/26) of octreotide LAR patients. Safety profile of both agents was consistent from extension baseline was seen in 54.3% (25/46) of pasireotide LAR and 42.3% (11/26) of octreotide LAR patients. Safety profile of both agents was consistent from extension baseline was seen in 54.3% (25/46) of pasireotide LAR and 42.3% (11/26) of octreotide LAR patients. Safety profile of both agents was consistent from extension baseline.

Conclusions
Pasireotide LAR holds promise as a treatment option for acromegaly patients inadequately controlled with octreotide LAR. Hyperglycemia associated with pasireotide LAR appeared to be reversible upon discontinuation of pasireotide.

DOI: 10.1530/endoabs.32.P847

P848
Advanced glycation end product associated skin autofluorescence and serum corboxymethyl lysine levels in acromegaly

Dilek Gogas Yazuv1, Serap Yalin2, Dilek Yazici3, Mehmet Yasar4 & Oguzhan Deyneli5

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

Aim
Nonenzymatic advanced glycation and oxidation end-products, advanced glycation end-products (AGEs), impart a potent impact on vessels in diabetic state and in euglycemic conditions with increased oxidative stress. The aim of this study is to measure AGEs and its relationship with carotid intima media thickness (CIMT) in acromegaly patients.

Method
A case-control study was performed in 225 acromegalic patients (F/M: 116/109, 50.6±11 years.) and age and sex matched 100 controls (F/M: 58/42, 52.6±11 years.). Skin autofluorescence (SAF) is a validated noninvasive measure of tissue AGEs SAF was measured with the AGE Reader. Serum carboxymethyl lysine (CML) was measured by HPLC and immunochromiluminescence method respectively. CIMT was assessed with Doppler ultrasonography.

Results
SAF was higher in acromegalic patients (1.95±0.32 arbitrary units (AU) compared with controls (1.62±0.33 AU) (P = 0.003). serum CML levels were higher in acromegalic (0.245±0.11 ng/dl) compared with controls (0.175±0.07 ng/dl) (P = 0.002). CIMT measures were 0.62±0.14 and 0.59±0.14 mm for acromegalic and control groups respectively (P < 0.0001). Correlation analysis showed a positive correlation between SAF and serum CML (r = −0.35, P = 0.002), CIMT (r = 0.25, P = 0.004) and serum growth hormone levels (r = −0.33, P = 0.03). sCML levels were higher in uncontrolled acromegalic compared to uncontrolled patients. Accumulation of tissue AGEs is increased in acromegalic patients.

Table 1 SAF, sCML and A1c levels in diabetic and non diabetic acromegalic patients

<table>
<thead>
<tr>
<th></th>
<th>Diabetes (+) acromegalic patients</th>
<th>Diabetes (−) acromegalic patients</th>
<th>Control group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c(%)</td>
<td>7.05 ± 1.1</td>
<td>5.4 ± 0.6</td>
<td>5.4 ± 0.4</td>
<td>0.001</td>
</tr>
<tr>
<td>SAF (AU)</td>
<td>1.93 ± 0.3</td>
<td>1.88 ± 0.6</td>
<td>1.62 ± 0.37</td>
<td>0.01</td>
</tr>
<tr>
<td>sCML (ng/dl)</td>
<td>0.245 ± 0.11</td>
<td>0.172 ± 0.06</td>
<td>0.174 ± 0.12</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Conclusion
SAF and sCML levels increased in acromegalic patients regardless of hyperglycemia. AGE may have a role in the cardiovascular outcomes of acromegalic patients.

DOI: 10.1530/endoabs.32.P848

P849
The prevalence of insufficient test responses in patients with traumatic brain injury compared to healthy controls – results from The Danish National Study on posttraumatic hypopituitarism

Marianne Klose1, Peter Laurberg2, Louise Frederiksen3, Kirstine Stochoholm4, Jurgita Janukonyte´4, Jens Sandahl Christiansen4,5, Marianne Andersen3 & Ulla Feldt-Rasmussen6

1Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; 2Aarhus University Hospital, Aarhus, Denmark; 3Odense University Hospital, Odense, Denmark; 4Aalborg University Hospital, Aalborg, Denmark.

Introduction
We questioned the justification of general recommendations for assessment of hypopituitarism in patients with traumatic brain injury (TBI), and aimed to describe the prevalence of hypopituitarism in a national TBI population of patients admitted to a Danish hospital in 2008, as compared to healthy controls.

Patients and methods
We included 463 patients (18–65 years) hospitalized ≥ 24 h, with more than subtle TBI as indicated by loss of consciousness, amnesia, or cranial/cerebral imaging abnormalities. The patients underwent endocrine assessment median 2.5

Endocrine Abstracts (2013) Vol 32
Endocrine Abstracts (2013) Vol 32

P850

Endoscopic transphenoidal approach as a promising surgical option in the treatment of craniopharyngioma
Marco Faustini-Fustini1, Matteo Zoli2, Diego Mazzatenta2, Daniele Santi3, Giulia Brigante1, Ernesto Pasquini4 & Giorgio Franks5
1Endocrine Unit, Department of Medicine, Bellaria Hospital, Bologna, Italy; 2Neurosurgery, IRCCS Institute of Neurological Sciences, Bologna, Italy; 3Endocrine Unit, University of Modena and Reggio Emilia, Modena, Italy; 4ENT Department, University of Bologna, Bologna, Italy.

Introduction
The management of craniopharyngioma (CR) remains a challenge. The introduction of endoscopic techniques in the surgical approach to the sella/suprasellar region would have profound implications for treatment. The aim of the study was to analyze results, advantages and limits of endoscopic endonasal approach (EEA).

Design/methods
From 1998 to 2012, 95 patients underwent surgery for CR. Trancranial approach was chosen for 33 patients (35%) on the basis of shape, size, and location. The remaining 62 (52% sellar and suprasellar, 45% purely suprasellar, 3% purely intrasellar; male to female ratio: 0.73; median age: 46 years, range, 3–83 years; 26% aged 18 years or younger) were operated by EEA, for a total of 71 surgical procedures, including nine recurrences during the follow-up period (mean: 59 months, range, 3–98 months).

Results
At presentation, visual impairment was detected in 77%, hypopituitarism in 54%, isolated diabetes insipidus in 3% of cases, panhypopituitarism coupled with DI in 24%. Endocrine function became further worse postoperatively, as expected (novel cases of DI and hypopituitarism occurred in 12.6 and 15.4%, respectively); conversely, after EEA visual function returned to normal in 35%, improved in 47%, and remained unchanged in 18%. Gross tumor removal was obtained in 80%. Morbidity consisted in post-operative CSF leak (18%) and chronic subdural hematoma (1.5%); one acute post-operative hydrocephalus (1.5%) was fatal. Weight gain occurred in 6%. Recurrence rate was 14.5%. Quality of life was preserved in 85% of cases, a moderate worsening (social reintegration at a lower level) occurred in 10% and a heavy worsening (semi- or totally dependent) in 5%.

Conclusions
EEA was a reliable approach in the majority of patients (65%) referred to us. The technique, safe and well tolerated, provides a direct approach along the way of the tumor growth and allows the surgeon to remove the lesion, avoiding brain retraction and vascular-nervous structures manipulation.

DOI: 10.1530/endoabs.32.P850

P851

A precocious GH peak at GHRH plus arginine test in GH sufficient short children is predictive of a lower growth velocity
Flavia Prodani1,2, Matteo Castagno3, Simonetta Bellone1, Giulia Genoni1, Enrico Giglione4, Agostina Marolda1, Antonella Petri1, Gianluca Aimearetti1 & Gianni Bona1
1Endocrine Unit, University of Modena and Reggio Emilia, Modena, Italy; 2Department of Neurosurgery, IRCCS Institute of Neurological Sciences, Bologna, Italy; 3Endocrine Unit, Department of Medicine, Bellaria Hospital, Bologna, Italy; 4Endocrine Unit, University of Modena and Reggio Emilia, Modena, Italy.

Introduction
GH secretion is considered adequate when at least one value is >20 ng/ml at the GHRH + arginine (ARG) test. Because GH typically peaks at 45 min, we evaluated whether peak occurrence at one specific time is predictive of clinical outcomes in short stature children who are GH sufficient. Subjects and methods
Children who performed a GHRH plus ARG test for short stature were retrospectively recruited. Inclusion criteria were: i) a GH peak >20 ng/ml; ii) Tanner stages within 1–3 stages; iii) 1 year growth velocity (GV) since the test execution; iv) born adequate for gestational age; v) the absence of signs suggestive of syndromes. Primary outcomes were height standard deviation score (SDS), GV, GV SDS and IGF-I SDS.

Results
A 228 subjects were recruited, by which 14 were excluded because they did not satisfy inclusion criteria. Of 214 subjects, 121 (56.5%) had a peak at 45 min, 55 (25.7%) at 30 min, and 38 (17.8%) at 60 min. Subjects presented a peak at 30 min had lower height SDS (P < 0.05), GV (P < 0.001), GV SDS (P < 0.001), and GH peak (P < 0.05) than those had a peak at 45 min. Subjects presented a peak at 30 min had lower GV (P < 0.001), and GV SDS (P < 0.001), but higher GH peak (P < 0.05) than those had a peak at 60 min. No differences were shown between children with a peak at 45 or 60 min. No differences in Tanner stages, sex, IGF-I SDS were recorded among three groups.

Conclusion
A peak at 30 min at the GHRH + ARG test in children who are short and without GH deficiency may be predictive of lower GV in the year of the test. Because ARG infusion stops at 30 min, a somatostatinergetic higher tone could have a role in the clinical picture.

DOI: 10.1530/endoabs.32.P851

P852

A novel mutation in gonadotropin releasing hormone receptor causing delay in puberty in a sporadic case of isolated hypogonadotropic hypogonadism
Misbah Riaz1, Qaiser Mansoor2, Maleeha Akram1, Madihah Shabbaz2, Shaista Aslam1, Shakeel Mirza1, Irfanullah3, Parveen Akhtar3, Mazhar Quayum4, Afzaal Ahmed Nasveen5, Fahim Tahir5, Muhammad Ihsani6 & S S R Rizvi1
1Department of Zoology, PMAS Arid Agriculture University, Rawalpindi, Pakistan; 2Institute of Biomedical and Genetic Engineering (IBGE), Islamabad, Pakistan; 3Department of Zoology, Government College University, Lahore, Pakistan; 4Department of Medicine, Military Hospital, Rawalpindi, Pakistan; 5Pakistan Institute of Sciences (PIMS), Islamabad, Pakistan; 6Department of Pediatrics, Foji Foundation Hospital, Rawalpindi, Pakistan; 7Department of Reproductive Physiology, National Institute of Health, Islamabad, Pakistan; 8Pakistan Science Foundation, Islamabad, Pakistan.

The signaling of G protein-coupled receptor 54 (GPR54) is a key regulator of the secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamic GnRH neurons, whereas GnRH is a crucial neurohormone regulating the secretion of FSH and LH at the time of puberty. The deficiency in the release or action of GnRH leads to hypogonadotropic hypogonadism (HH) characterized by low FSH, LH and testosterone (T) and results in absent or impaired sexual development at puberty. In boys, the absence of the signs of sexual maturation at the age of 15 years is referred to as delayed puberty. Amongst others, mutations in GPR54 and GnRH receptor (GnRHR) are possible causes of HH. The present study was designed to determine the role of mutations in GPR54 and GnRHR genes in causing HH in Pakistani boys. Thirty-one patients with delayed puberty...
and 31 normal age matched controls were included in the study. Genomic DNA was extracted and amplified by PCR using specific primers for GPR54 and GnRHR splice site exons. Mutations were analyzed by single-stranded conformation polymorphism and sequencing. No mutation was identified in GPR54 gene, while two mutations in GnRHR gene were observed in one sporadic case of isolated HH. One was T to G synonymous mutation at nucleotide position 123, which did not cause substitution of valine with any other amino acid. The other mutation at position 101 of the neucleotide was a missense mutation, which substituted serine with phenylalanine at 34th position of the extracellular domain of the GnRHR. This mutation, Ser34Phe, observed in 16 years old boy, caused low concentrations of FSH, LH and T and possibly delayed his puberty. In conclusion, the present study demonstrates that mutations in GnRHR may play a role in delaying male puberty in our local population.

DOI: 10.1530/endoabs.32.P854

P853
Evaluation of late-night salivary cortisol during a Phase III study with pasireotide in patients with Cushing’s disease
John Newell-Price1, Stephan Petersen2, Rosario Pivonello3, James Findling4, Maria Fleseriu5, Andrew Trovato6, Gareth Hughes7, Monica Ligueros-Saylan7 & Beverly Biller8
1University of Sheffield, Sheffield, UK; 2ENDOCenter for Endocrine Tumors, Hamburg, Germany; 3Federico II University, Naples, Italy; 4Medical College of Wisconsin, Milwaukee, Wisconsin, USA; 5Oregon Health & Science University, Portland, Oregon, USA; 6Novartis Pharma AG, Basel, Switzerland; 7Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA; 8Massachusetts General Hospital, Boston, Massachusetts, USA.

Introduction
Measurement of salivary cortisol is a simple, convenient, accurate and reproducible technique with potential value during the diagnosis/management of hypercortisolism. Current analysis evaluates changes in late-night salivary cortisol (LNSC) during pasireotide treatment in patients with Cushing’s disease (CD).

Methods
A 12 m, Phase III study enrolled 162 adults with confirmed hypercortisolism patients with CD) during pasireotide treatment in patients with Cushing’s disease (CD).

Results
Baseline LNSC was measured in 93 patients; median levels were 17.3 and 10.3 nmol/l in the 600 µg/900 µg s.c. bid. LNSC assessment (assay: cortisol ELISA RES5261, IBL-Hamburg GmbH, Germany) was an exploratory objective based on a single, optional measurement at midnight ± 1 h on the same day as one of the 24-h UFC measurements. UFC control: UFC ≤ ULN; partial UFC control: UFC > ULN and ≥ 50% decrease from baseline.

Conclusions
Pasireotide decreased LNSC levels during 12 m of treatment. Salivary cortisol may be a simpler and more convenient biomarker than 24-h UFC to assess hypercortisolism patients with CD; further studies are required.

DOI: 10.1530/endoabs.32.P853

P854
Evaluation of long-term pituitary functions after hypoxia due to ventricular arrhythmias: a preliminary report
Fatih Tanriverdi1, Yasin Simek1, Mehmet Gungor Kaya2, Beren Calapkorus2, Halit Dur1, Zuleyha Karaca1, Kursad Uluhuzarci1 & Fahrettin Kestemir3
1Erciyes University Medical School, Kayseri, Turkey; 2Erciyes University Medical School, Department of Cardiology, Kayseri, Turkey.

Introduction:
Traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), stroke and cerebrovascular disease (CVD) are identified as risk factors for hypothalamic dysfunction. However, the mechanisms and the risk factors for the hypothalamo-pituitary dysfunction due to TBI, SAH, stroke and CVD are still unclear (1,2,3). Hypoxia, hypoxemia, neuroinflammation, autoimmunity could have impact in the pathogenesis (4). In patients with serious ventricular arrhythmias who need resuscitation, brain tissue may be exposed to short-term severe ischemia and hypoxia. However there are no data in the literature regarding pituitary dysfunction after ventricular arrhythmias.

Materials and methods
Thirty patients with ventricular arrhythmias (25 male, five female) were included in the study. Basal hormone levels were measured. To assess GH – insulin like growth factor (IGF-1) axis glucagon stimulation test was performed and 1 µg ACTH stimulation test was used for assessing hypothalamic-pituitary-adrenal axis.

Results
Four patients had secondary hypogonadism (13.3%). When the two stimulation tests and basal hormone levels were evaluated together no patient had ACTH deficiency, but glucagon stimulation test revealed GH deficiency in 8 of 30 (26.6%) patients. There were no statistical difference according to age, BMI, IGF-1 levels and other hormone levels between GH deficiency and GH sufficient group. However, IGF-1 levels were significantly lower in GH deficiency group.

Discussion
In conclusion, present data clearly suggest that in patients with serious ventricular arrhythmias who need cardiac resuscitation, pituitary dysfunction is not uncommon. Future studies need to be done to understand whether routine screening of pituitary functions in this patient group is clinically relevant or not.

DOI: 10.1530/endoabs.32.P854

P855
Long-term efficacy of long-acting somatostatin analogues in combination with pegvisomant in 112 acromegaly patients, a retrospective single centre study with follow up for up to 8 years
Sanne Franck, Aart-Jan van der Lely, Yolanda de Rijke & Sebastian Neggers
Erasmus Medical Centre, Rotterdam, The Netherlands.

Introduction
Pegvisomant (PEGV) has an efficacy of >90% to control insulin-like growth factor (IGF-1), however in everyday practice a limited efficacy of 63% was reported.

Aim
To assess efficacy in the largest single center cohort of acromegalis using PEGV.

Methods
A 112 subjects (65 male) were not controlled with high-dose somatostatin analogues (LA-SRIF) for at least 6 months. To control acromegaly, 109 subjects added PEGV and three used PEGV alone. IGF-1 and GH levels (start, lowest and last values) were retrospectively re-assessed in a single run. IGF-1 was measured by the Immulite2000 and GH by the IDS-iSYS immuno-assay, to assess GH without interference of PEGV. Results are expressed as median (interquartile range). At baseline 80% of the subjects (age 47.3 years (38.4–59.0)) had a macro-adenoma.

Results
Duration of PEGV treatment was 4.0 years (1.9–6.2). Normalization of IGF-1 was observed in 96%, with an IGF-1 of 17.9 nmol/l (13.0–23.8) and a ratio IGF-1 of 0.6 (0.4–0.7). At the last visit, weekly PEGV dose of 80 mg (60–120 mg) was used during combination treatment with LA-SRIFs. In patients with monotherapy a weekly PEGV dose of 210 mg (125–280 mg) was used. No significant differences in PEGV dose, needed to control IGF-1 were observed between sexes, diabetic/non-diabetic patients, surgery/non-surgery and Gilberts
polymorphism/non-Gilberts polymorphism. Baseline GH levels (on LA-SRIFs) were not significantly different compared with GH during PEGV and LA-SRIFs treatment (P=0.567). Two subgroups were defined according to surgical status (surgery vs non-surgery). After surgery GH seem to decrease during treatment (8.7 and 4.5 nmol/l), while primary medical treatment GH seem to increase (4.0 and 4.5 nmol/l), although not significantly different (P=0.091 (post-radiotherapy-group was excluded)).

Conclusion
Combination of LA-SRIF and PEGV in acromegaly is effective up to 8 years, with an efficacy of 96%. GH levels do not change during treatment.
DOI: 10.1530/endoabs.32.P855

P856
Long-term safety of long-acting somatostatin analogues in combination with pegvisomant in 133 acromegalic patients, a retrospective single centre study with follow up for up to 8 years
Sanne Franck, Aart-Jan van der Lely, Rita Koole, Felix de Rooij & Sebastian Neggers
Erasmus medical centre, Rotterdam, The Netherlands.

Introduction
Pegvisomant (PEGV) has an efficacy of >90% to control insulin-like growth factor-1. Main safety issues are elevated transaminases that seem to be related to Gilbert’s polymorphisms (GiPism) or gender and tumor-size increase (1).

Aim
To assess safety in the largest single center cohort of acromegalics using PEGV.

Methods
Results are expressed as median (interquartile-range).

One-hundred and thirty-three acromegaly patients (73 males) used PEGV and long-acting somatostatin analogues LA-SRIF, to control active disease (n=112) or to enhance quality of life (n=21), over a period of 4.0 years (1.9–6.2).

Results
At baseline, 79% of the subjects (age, 49.1 years (39.3–59.2)) had a macroadroma. Transient dose independent elevated transaminases (TDIET) of more than three times the upper limit of normal (>3x ULN) were observed in 20 patients (15%), they resolved without PEGV dose adaptation. One patient discontinued PEGV, as previously reported (2). Biliary tract disease could explain at least two of these cases, so 14% could be linked to PEGV use. TDIET >3x ULN occurred after 5.2 months (3.0–15.9) and normalised in 3.9 months (2.8–5.1).

Re-exposure to PEGV after discontinuation resulted in a second period of TDIET in two patients.

GiPism was found in 68 (54%) of 122 tested patients, 11% homozygous and 45% heterozygous. Of the 20 TDIET cases, 15% were homozygous and seven (35%) were heterozygous. No association between GiPism and developing TDIET was found in patients with heterozygous (P=0.59) or homozygous polymorphism (P=0.36) compared with non-GiPism or gender (P=0.08).

Tumour-size decrease was observed in 12% but size could not be evaluated in 14 patients due to an empty sella. One patient needed surgery due to tumour-size increase.

Conclusion
Combination of LA-SRIF and PEGV in acromegaly is safe up to 8 years. TDIET are observed in 15% of acromegalics. TDIET are not related to GiPism or gender. In 12% tumour size decrease occurred.
DOI: 10.1530/endoabs.32.P856

P857
Similar response to therapy of pituitary adenomas with and without SOX2-expressing cells
Mihail Coculescu1-2, Anca Campean3, Cristina Stanu1, Cristina Capatina1, Monica Livia Gheorghiu1, Andra Carageorgheopol4, Dan Hortopan5, Vasile Ciubotaru6 & Marius Raica1

Introduction
SOX2 is an early developmental transcription factor and a marker for pituitary progenitor cells. The study aimed to investigate if the pituitary adenomas with positive SOX2 immuno-reactivity shows a different response to therapy as compared with controls.

Patients and methods
We investigated 15 pituitary macroadenomas, eight with SOX2 immunoreactivity (SOX2+) and seven without (SOX2–) controls; five were GH producing tumours (three SOX2–, two SOX2+), five prolactinomas (four SOX2–, one SOX2+) and five non-functioning pituitary tumours (one SOX2+, four SOX2–) confirmed by immunohistochemistry, ABC method. Anterior pituitary hormones were measured in simultaneously sampled serum and cerebrospinal fluid (CSF) by fluorimunnoassay with europium. Three patients with SOX+ and three SOX– adenomas showed high CSF:serum ratio for one or two hormones (five of them for FSH and/or LH and one for prolactin). The tumour volume was appreciated by CT or MRI.

Results
All pituitary adenomas were partially removed by surgery. Additional treatment were i) high-voltage radiotherapy or gamma knife (two SOX+ and three SOX– tumours); ii) radiotherapy associated with medical treatment with somatostatin analogs and/or dopaminergic agonist cabergoline (four SOX+ and one SOX– tumours); iii) only medical treatment (one SOX+ and two SOX– tumours). The average follow-up was 53.3 months.

From first group A with radiotherapy, both SOX2+ pituitary adenomas were cured and there was upper 50% decrease in tumour volume in two SOX2+ pituitary adenomas. Patients with triple therapy (B) need high doses of dopaminergic agonists and somatostatin analogs. Both, tumour volume and hormone secretion decreased when drug therapy started after radiotherapy (the tumour volume decreased more than 50% in two SOX+ and one SOX– tumour and lower than 50% in two SOX+ adenomas).

Conclusion
Pituitary macroadenomas with SOX2-positive cells are not refractory to treatment and showed similar responses to radiotherapy oral medication (somatostatin analogues or cabergoline) as the controls.
DOI: 10.1530/endoabs.32.P857
P858
The clinical characteristics of pain in patients with pituitary adenomas
Christina Dimopoulou1,2, Anastasia Athanasoulia1, Erik Hanisch1, Stefanie Held1, Thomas Toelle1, Till Sprenger1, Walter Zieglausberger1, Hildegard Pflister1, Josephine Roemmler1, Jochen Schoepfl1, Guenter Stall1 & Caroline Stevers1
1Max Planck Institute of Psychiatry, Munich, Germany; 2Medizinische Klinik IV, Ludwig-Maximilians-University, Munich, Germany; Department of Neurology, Technische Universität München, Munich, Germany.

Introduction
Clinical presentation of pituitary adenomas frequently involves pain, particularly headache, probably due to both structural and functional properties of the tumour.

Design
In a retrospective analysis, we investigated clinical characteristics of pain in 277 patients with pituitary disease (n=81 acromegaly; n=50 Cushing’s disease; n=86 prolactinoma; n=60 non-functioning pituitary adenoma). Specific pain patterns were measured using three standardised pain questionnaires, MIDAS (Migraine Disability Assessment), the painDETECT and the DQSS (German Society for the Study of Pain) questionnaire.

Results
For the whole group, 156 tumours were macroadenomas (56%) and 121 were microadenomas (44%). Cavernous sinus invasion was observed in 55 tumours (20%). The commonest tumour associated with pain was adrenocorticotrophic adenoma (n=17; 34%), followed by growth hormone secreting (n=23; 28%), prolactinoma (n=20; 23%) and non-functioning pituitary adenoma (n=8; 13%).

Primary pain site was located in the lower back/bottom region (68.2%) and in the mouth/face/head region (61.9%). Regarding pain quality and severity, the majority of the pituitary patients (89%) described their pain as ‘depress’ or ‘in contrast’ to ‘surface’ pain and reported on a scale of 0 (= no pain) to 10 (= most severe pain) a median pain intensity of 3 (IQR 3.0–6.0) within the last 4 weeks. Pituitary patients presented primarily with an episodic (46%) followed by a permanent/chronic (30%) pain component. Most common pain-associated features comprised noise sensitivity (67.9%), visual disturbances (64%), photophobia (35%) and nausea (53.8%). Both physical (81.4%) and emotional stress (46.5%) were reported to trigger pain. Tumour-associated headache leads to severe levels of disability in daily life in a minority of patients (13.5%).

Conclusion
Pain appears to be a significant problem in pituitary disease and is associated with a range of pain phenotypes. A combination of factors including tumour activity, cavernous sinus invasion, as well as previous predisposition to pain might play a role in pain phenotypes.

DOI: 10.1530/endoboa.32.P858

P859
Genetic and clinical characteristics of Serbian FIPA families
Dragana Miljic1, Sandra Pekic1, Marko Stojanic1, Nadezhda Dzeranova2, Judit Denes3, Plamena Gabrovska4, Marta Korbonits5 & Vera Popovic1
1Clinic for Endocrinology, University Clinical Center, Faculty of Medicine, Belgrade University, Belgrade, Serbia; 2Department of Endocrinology, Barts and the London School of Medicine, Queen Mary University of London, London, EC1M 6BQ, UK.

Introduction
Recently, major advances have been made in genetics of familial acromegaly and isolated pituitary adenoma (FIPA). Mutations in the aryl hydrocarbon interacting protein (AIP) gene have been found in 25–50% of patients with FIPA and familial acromegaly.

Aim of the study
Our goal was to identify and collect data on patients who met the criteria for FIPA.

Patients and methods
The patients were identified between 2008–2012 in the Clinical Center of Serbia, Belgrade. Genetic analysis of AIP gene was performed as part of the International FIPA Consortium project. All patients signed informed consent for genetic testing before entering the study.

Results
In 24 families, 51 subjects (31F/20M) with FIPA were identified. Four GH families (two with gigantism), four PRL, two NFPA, five NFPA-PRL, three GH-PRL, four GH-NFPA, one GH-PRL-NFPA and one PRL-ACTH were registered. Average age at diagnosis for patients with mutations in the AIP gene was 26 ± 23 years compared to 38 ± 12 years for AIP mutation-negative group. Median age at diagnosis was 14 for gigantism, 32 for prolactinoma, 35 for acromegaly and 50 for NFPA. In male patients, 75% were macroadenomas compared to 45% in female patients. So far, 15 families have been screened for AIP mutations. In 13% (two patients with gigantism and one with NFPA), AIP mutations/deletions were registered.

Conclusion
So far, our results indicate that prevalence of AIP gene mutations in Serbian FIPA patients is around 13%. Further genetic testing is needed for AIP gene mutations. Other genetic causes, which may be involved also need to be investigated.

DOI: 10.1530/endoboa.32.P859

P860
Doubled mortality ratio in female patients with non-functioning pituitary adenomas
Simona Galou1,2, Ionela Baciu1, Sorin Ioacara1, Monica Gheorghiu1,2, Corin Badu1,2, Catalina Poiana1,2 & Mihutil Coculescu1
1“Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania; 2“C. I. Parhon” Institute of Endocrinology, Bucharest, Romania; 3N. Paulescu” National Institute of Diabetes, Nutrition and Metabolic Diseases, Bucharest, Romania.

Introduction
Patients with non-functioning pituitary adenomas (NFPA) and hypopituitarism had a reduced life expectancy.

Aims
To assess mortality ratio and to identify prognostic factors associated with mortality in patients with NFPA in the last decade.

Methods
A 196 patients (83 F/113 M, mean age 52.7 ± 9.0 years) with NFPA admitted in a single Neuroendocrinology Department between January 2001 and December 2010 were retrospectively studied. PAMCOMP computation program was used to calculate standardized mortality ratio (SMR). Cox regression analysis revealed independent factors associated with mortality.

Results
During follow-up (median 7.5 years–1298.04 person years), 26 patients died, corresponding to a death rate of 20 deaths/1000 person years. Statistically significant more patients with hypopituitarism for at least one axis deceased (22/156, 14.10%), as compared with patients without pituitary failure (1/22 patient deceased – 2.07%), P=0.03. All causes mortality was not statistically different from that of general population: Standardized mortality ratio (SMR) was 1.2 (95% confidence interval (CI) 0.83–1.86). Females had a doubled mortality ratio: SMR 2.03 (95% CI 1.01–3.64), but males had a mortality ratio similar to general population. SMR 0.87 (95% CI 0.48–1.44). When assessed by Cox-regression analysis, prednisone dose for corticosteroid insufficiency (HR 1.5 (95% CI 1.18–1.98)) and last systolic blood pressure (HR 1.04 (95% CI 1.00–1.081)) were independent predictors of mortality in females. Mortality rose progressively with prednisone dose (log rank: P=0.007) in females, but not in males (log rank: P=0.197).

Conclusions
Females with non-functioning pituitary adenomas and hypopituitarism had a doubled mortality ratio as compared with general population, influenced by prednisone dose used for substitution and systolic blood pressure.

DOI: 10.1530/endoboa.32.P860

P861
Incidentally discovered pituitary adenomas: single-center experience on 205 patients
Elena Malchiodi, Emanuele Ferrante, Giovanna Mantovani, Alessandra Toini, Elisa Sala, Elisa Verrua, Claudia Giavoli, Elena Malchiodi, Emanuele Ferrante, Giovanna Mantovani, Alessandra Toini, Elisa Sala, Elisa Verrua, Claudia Giavoli, Marcello Filiponti, Anna Spada & Paolo Beck-Peccoz
Department of Clinical Sciences and Community Health, Endocrinology and Diabetology Unit, University of Milan, Fondazione IRCCS Ca Granda Ospedale Maggiore Policlinico, Milan, Italy.

Introduction
Pituitary incidentalomas are lesions discovered on an imaging study performed for an unrelated reason. Their frequency varies among 0.2–38% and it is continuously increasing due to the development of neuroimaging techniques. The aim of the study is to investigate clinical and biochemical characteristics of 205 consecutive patients (70% female, mean age 53.6 ± 18.2 years) with incidental pituitary adenoma (IPA) followed at our center from 1990 to present.

Methods
In all patients, hormonal evaluation (basal anteropituitary function, ACTH imaging were performed at baseline, 6 months later and then annually if there was
no other specific indication. Seventy patients were also screened for subclinical hypercortisolism (cortisol after 1 mg overnight dexamethasone suppression test (1 mg DST), late-night salivary cortisol, 24-hours urinary free cortisol).

Results
At diagnosis, 39% of patients had macroadenomas. One or more pituitary deficiencies were observed in 14.3% of cases (macro 28.6 vs micro 5.6%, \( P < 0.05 \)). Hyperprolactinemia (\( < 100 \text{ ng/ml} \)) was observed in 13.9% of patients (macro 15.5 vs micro 12.8%, \( P \text{NS} \)). Subclinical hypercortisolism was found in 3/70 (4.2%) patients studied, all with macroadenomas. One hundred and ten patients had a follow-up longer than 12 months with a mean follow-up of 4.9 years. Radiological evaluation revealed a significant increase in tumor mass in 19/110 patients (17.3%, 13 macro vs 6 micro, \( P \text{NS} \)) and a reduction in 5.4% (all microadenomas). The volumetric increase occurred in 88% of patients during the first 2 years after diagnosis. Additional pituitary deficiencies were observed in 3% of patients during follow-up. Overall, 18% of patients were treated with transphenoidal adenectomy owing to initial mass size or for their rapid increase.

Conclusions
Our data confirm that patients with IPA need for a close radiological and hormonal follow-up. In addition, we suggest exclusion of subclinical hypercortisolism in such patients.

DOI: 10.1530/endo2013.3.P661

P862
Clinical diagnostic implications of sequential pattern of dynamic MRI for pituitary microadenoma
Qinghua Guo1, Dana Erickson1, William Young1, Irma Bancos1 & Bradley Erickson1
1Mayo Clinic, Rochester, Minnesota, USA; 2Chinese PLA General Hospital, Beijing, China.

Objective
We examined whether sequential enhancement patterns of pituitary microadenomas on dynamic MRI correlates with different subtypes of pituitary tumors.Materials and methods
Patients with pituitary microadenomas imaged via dynamic MRI between years 2000 and 2012 were included. The intensity of the adenoma and of normal gland at each time point in the dynamic sequence was measured by drawing a region of interest (ROI) on both the normal pituitary gland and the tumor. Measurements included: enhancement ratio (ER), defined as the ratio of the tissue at time \( t \) vs the baseline \( (t = 0) \); pituitary-adenoma ratio (PAR), which is the ratio of the normal anterior pituitary lobe to that of pituitary adenoma; and, the speed to reach the peak intensity. From these data tumors were classified as early, simultaneous or late (peak before, at the same time or after normal pituitary tissue, respectively). Correlation between the enhancement pattern and the tumor subtype was analyzed using Pearson product-moment correlation coefficients and logistic regression analysis.

Results
A total of 118 patients had functional adenomas, while 47 patients had nonfunctional adenomas. We found that the enhancement levels in all pituitary adenomas subtypes were lower than those in normal pituitary tissue \( (P < 0.001) \). There was a significant correlation between the enhancement patterns of functioning vs nonfunctioning tumors \( (P = 0.0397) \) and between the four tumor subtypes \( (P = 0.0039) \). Functional adenomas usually exhibited simultaneous or late enhancement pattern while nonfunctional adenomas showed early enhancement pattern. The time to reach peak enhancement in normal pituitary tissue was shorter nonfunctioning adenomas \( (P = 0.0082) \) and GH tumor group \( (P = 0.0042) \). Conclusion
Our study is the first to show significant correlation between enhancement pattern and pituitary adenoma subtype. This finding can provide supplemental information in differential diagnosis of pituitary microadenomas as well as guide future studies of appropriate timing of image acquisition according to tumor subtypes.

DOI: 10.1530/endo2013.3.P662

P863
How to get surgical remission rates in ACTH- and GH-microadenomas to 100%
Dieter Ludecke1, Joerg Flitsch1, Patricia Crock2 & Wolfgang Saeger1
1University Hospital, Hamburg, Hamburg, Germany; 2University of Newcastle, Newcastle, New South Wales, Australia.

Introduction
Pharmacological treatments are available for all functioning pituitary adenomas, but found to be only ideal in prolactinomas. Therefore, at least in ACTH- and GH-microadenomas we have to strive to achieve 100% remission with transnasal surgery. Our question is, which combination of an increasing arsenal of pre- and peri-operative methods will bring the pituitary surgeons to this result without increasing complications.

Materials and methods
Data from published series of the author will be compared with new data from recent series. All patients had been operated, when MRI and direct transnasal micro-surgery were established. Special diagnostic methods: pretreatment with somatostatin analogs and GH-receptor blocker; intra- and extraoperative hormone measurements; intra-operative micro-histology; micro-doppler; neuro-navigation; as well as the importance of a micro-suction irrigation system for visualization and minimization of trauma, will be described and illustrated.

Results
ACTH-micro-adenomas: since introducing more refined diagnostic tests and cavernous sinus sampling, nearly all micro-adenomas were initially detected. Nevertheless, in a few cases early re-surgeries became necessary to achieve remissions. This was especially evident and important in children with Cushing syndrome (\( n = 100 \)). GH-microadenomas: in 2001 we published 100% remission in patients pretreated with somatostatin analogs vs 93% without pretreatment. This was statistically not significant, but of importance for the patients. Only rarely were intra-operative GH measurements influential in the group of microadenomas. In the last series from 2001 - 2005 without intra-operative GH-measurement and a long follow-up (mean > 5 years), a clear biochemical remission was surgically achieved in all 25 microadenomas. The majority was pretreated with somatostatin. Complications were rare, minor and transient.

Conclusions
Using advanced surgical micro-techniques, enhanced by immediate feedback of the surgical success with hormone measurements, our long-term remission rates are definitely superior to most published data with medical and/or radio-surgical treatment. There is a great benefit for patients and minimizes costs. 

DOI: 10.1530/endo2013.3.P663

P864
Moderate hyponatremia is associated with an increased risk of overall mortality: a comprehensive meta-analysis
Giovanni Corona1, Corinna Giulian1, Gabriele Parenti1, Dario Norello2, Joseph G Verbalis3, Gianni Forti1, Mario Maggi1 & Alessandro Per1
1Endocrinology Unit, Medical Department, Maggiore-Bellaria Hospital, Azienda Usl di Bologna, Bologna, Italy; 2Endocrinology Unit, Center for Research, Transfer and High Education on Chronic, Inflammatory, Degenerative and Neoplastic Disorders for the Development of Novel Therapies (DENOThe), Department of Clinic, Florence, Italy; 3Division of Endocrinology and Metabolism, Georgetown University, Washington DC, USA; 4Sexual Medicine and Andrology Unit, University of Florence, Florence, Italy.

Introduction
Hyponatremia is the most common electrolyte disorder in clinical practice, and evidence to date indicates that severe hyponatremia is associated with increased morbidity and mortality. The aim of our study was to perform a comprehensive meta-analysis that included all the published studies that compared mortality rates in subjects with or without hyponatremia of any degree.

Methods
An extensive Medline, Embase, and Cochrane search was performed to retrieve all studies published up to October 1, 2012 using the words 'hyponatremia' and 'mortality'.

Results
Eighty-one studies satisfied inclusion criteria encompassing a total of 850 222 patients, of whom 147 948 (17.4%) were hyponatremic. Across all 81 studies, hyponatremia was significantly associated with an increased risk of overall mortality (RR = 2.60 (2.31–2.93)). Hyponatremia was also found to increase the risk of mortality in patients with multiple diseases, including myocardial infarction (RR = 2.83 (2.23–3.58)), heart failure (RR = 2.47 (2.09–2.92)), cirrhosis (RR = 3.34 (1.91–5.83)), pulmonary infections (RR = 2.49 (1.44–4.30)), mixed diseases (RR = 2.50 (1.97–3.18)), and in hospitalized patients in whom the diagnosis was not specified (RR = 2.48 (2.09–2.45)). A mean difference of serum (Na +) of 4.8 mmol/l was found in subjects who eventually died compared to survivors (130.1 ± 5.6 vs 134.9 ± 5.1 mmol/l, \( P < 0.001 \)). Furthermore, a meta-regression analysis showed that the hyponatremia-related risk of overall mortality was inversely correlated with serum (Na +) (S = −0.096 (−0.114, −0.077); I² = 13–710 (12.258–16.161); both \( P < 0.0001 \)). This association was confirmed in a multiple regression model after adjusting for age, sex, and associated morbidities such as diabetes mellitus.
**P865**

**Effects of somatostatin analogues on muscle sympathetic nerve activity in acromegaly**

Chiara Carzaniga1, Gino Seravalle2, Roberto Attanasio3, Guido Grassi4, Renato Cozzi5, Letizia Maria Fatti6, Marcella Montini7, Giovanni Vitale8,9, Giovanni Sciotto4, Sarah Dumanti1, Massimo Scacchi1,2, Giuseppe Manca1, Francesco Cavagnini1 & Luca Persani1,2

1Department of Clinical Sciences and Community Health University of Milan, Milan, Italy; 2Istituto Auxologico Italiano Ircs, Milan, Italy; 3Endocrinology Istituto Galeazzi, Milan, Italy; 4Department of Clinical Medicine and Prevention University of Milano Bicocca, Milan, Italy; 5Division of Endocrinology Ospedale Niguarda Ca’ Granda, Milan, Italy; 6Humanitas Gavazzeni, Bergamo, Italy; 7Subspecialty School of Geriatrics University of Milan, Milan, Italy; 8Laboratory of Neuroendocrine Research Istituto Auxologico Italiano, Milan, Italy.

Introduction

While searching for mechanisms contributing to the increased mortality of acromegaly, we have previously described an unexpected sympathoinhibition in newly diagnosed patients (Seravalle et al., Clin Endocrinol 77:262, 2012) and interpreted this finding as an adaptive phenomenon. It has also been shown that centrally administered somatostatin (SS) inhibits peripheral sympathetic outflow in rodents (Rettig et al., Am J Physiol 257:R588, 1989). Based on the above, we elected to study muscle sympathetic nerve activity (MSNA) in acromegalic patients before and during treatment with SS analogues (SSA).

Study

MSNA was directly measured by microneurography in the following groups of subjects: i) 24 newly diagnosed acromegalic (13 men and 11 women, mean age 45.5 ± 13.0 years); ii) 22 patients on SSA, 11 of whom (seven men and four women, mean age 52.4 ± 13.9 years) attaining biochemical control according to the currently accepted criteria and 11 (five men and six women, mean age 56.4 ± 17.5 years) not attaining biochemical control; iii) 17 normal-weight healthy women, mean age 49.1 ± 15.6 years.

**Results**

As expected, mean MSNA was significantly lower in untreated acromegalics than in control subjects (18.3 ± 8.9 vs 37.8 ± 6.60 bursts/min, P < 0.01). Patients on SSA, either with controlled or uncontrolled disease, displayed mean MSNA values (27.4 ± 8.24 and 31.6 ± 5.27 bursts/min respectively) significantly lower than those shown by controls (P < 0.01) but significantly higher than those found in untreated acromegals (P < 0.05). Mean MSNA values were not significantly different between controlled and uncontrolled SSA-treated patients.

**Comment**

The present study has confirmed the profound sympathoinhibition characterizing untreated acromegaly and has shown the reversibility of this alteration with the improvement of the disease. These preliminary data do not allow to unveil a possible role of SSA in these changes.

DOI: 10.1530/endoabs.32.P865

---

**P867**

**Real world data in acromegaly – a retrospective chart audit**

Diego Feroni1, Anna Forsythe1, William Ludlam2, Roberta Rondena3, Cherry Thomas4 & Monica Gadelha5

1Endocrinology Unit, DIIMi and Centre of Excellence for Biomedical Research, IRRCS-AOU San Martino – IST, University of Genova, Genova, Italy; 2Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; 3Novartis Farma SpA, Orrigio, VA, Italy; 4Division of Endocrinology, University of Palermo, Palermo, Italy; 5Clementino Fraga Filho University Hospital, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil.

Introduction

The ideal strategy and the role of the different therapeutic options in acromegaly remain unclear. This research focuses on observing treatment options, and the respective level of disease control in acromegaly.

Methods

A retrospective chart audit was conducted in US, France, Italy, and Brazil (September 2012). 97 endocrinologists completed structured case report forms for the 4 most recently-seen patients (two with somatostatin analogues (SSAs), two with pegvisomant (PegV) or PegV + SSAs), n = 380; those on the last choice of medical therapy ≥ 6 months were included in the analysis (n = 335). Patient demographics, comorbidities, treatment history, insulin-like growth factor type I (IGF-I) expressed as ULN-fold of age-related reference range, and symptoms were collected. Here we report the preliminary data related to disease management and IGF-I control.

Results

Of the 335 treated patients (mean age 51 yrs; 52% males), 193(58%) were treated with SSAs, 116(35%) with PegV, and 26(8%) with PegV + SSAs. 208 of 335 patients (62%) were treated with surgery prior to medical therapy (74% US, 63% Brazil, 54% France, 51% Italy); 127 (38%) received medical therapy with (n = 6) or without (n = 121) radiation. 63 of 208 (30%) patients treated with surgery prior to medical therapy and 66 of 127 (52%) treated with medical therapy had IGF-I > ULN. 20% of all study patients had IGF-I > 1.5xULN (19% US, 28% Brazil, 21% France, 15% Italy) despite treatments. 99% of SSA treated patients had IGF-I ≤ ULN, vs. 67% of patients on PegV and 73% on PegV + SSAs. The rates of acromegaly symptoms and comorbidities were similar among patients treated with SSAs and PegV. Incidence of paresthesia and perspiration were significantly lower in patients with IGF-I ≤ ULN (P < 0.05).

Conclusions

Medical therapy remains an integral component of acromegaly management. Despite the different therapeutic strategies, including different drugs, 30-52% of patients treated with cabergoline (CAB) on metabolic complications, metabolic syndrome (MS) prevalence and visceral adiposity index (VAI) in hyperprolactinemic patients.

Patients and methods

Seventy-one patients (51 F, 20 M, aged 35.4 ± 11.7 years), including 36 with microprolactinomas, 32 with macroprolactinomas and three with non-tumoral hyperprolactinemia entered the study. In all patients, PRL, and metabolic parameters (BMI, waist circumference, lipid and glucose profile, insulin, VAI) were assessed at diagnosis and after 12 and 60 months of continuous CAB treatment. MS was evaluated in line with NICE-ATP III criteria.

Results

Compared to baseline, CAB induced a significant decrease in PRL levels after 12 months (P = 0.000) and a further decrease after 60 months (P = 0.000) with complete normalization in 93% of patients. At baseline, MS prevalence was significantly higher in patients with PRL above than in those with PRL lower than the median (187 µg/L) (P = 0.02). MS prevalence significantly decreased after 12 months (12.6%; P = 0.009) and 60% (7% (P = 0.000) months of treatment compared to baseline (32.4%). Total cholesterol and triglycerides were significantly reduced after 12-month CAB compared to baseline (P = 0.03), and further decreased (P = 0.000) after 60-month follow-up. HDL-cholesterol resulted significantly increased after 60-month CAB compared to baseline (P = 0.000) and 12 months of CAB (P = 0.001) and were further improved after long-term CAB (P = 0.03 and P = 0.000 respectively) compared to short-term therapy. Compared to baseline, a slight but not significant decrease in VAI was found at 12-month evaluation, whereas VAI was significantly decreased after 60 months of treatment (P = 0.000).

Conclusions

Short-term CAB treatment significantly improves metabolic profile, so that to reduce MS prevalence, whereas longer treatment is required to achieve a significant improvement of VAI.

DOI: 10.1530/endoabs.32.P866

---

**P868**

**Effects of short (12 months) and long (60 months) term treatment with cabergoline on metabolic syndrome and visceral adiposity index in patients with hyperprolactinemia**

Renata S Auriemma1, Luciana Granieri1, Ylenia Perone1, Annamaria Colao1 & Rosario Pivonello1

1Endocrinology Unit, DiMI and Centre of Excellence for Biomedical Research, IRRCS-AOU San Martino – IST, University of Genova, Genova, Italy; 2Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; 3Novartis Farma SpA, Orrigio, VA, Italy; 4Division of Endocrinology, University of Palermo, Palermo, Italy.

Introduction

Hyperprolactinemia is reportedly associated with an impaired metabolic profile, particularly in patients with concomitant hypogonadism. The current study aimed at investigating the effects of short (12 months) and long (60 months) treatment with cabergoline (CAB) on metabolic complications, metabolic syndrome (MS) prevalence and visceral adiposity index (VAI) in hyperprolactinemic patients.

Patients and methods

Seventy-one patients (51 F, 20 M, aged 35.4 ± 11.7 years), including 36 with microprolactinomas, 32 with macroprolactinomas and three with non-tumoral hyperprolactinemia entered the study. In all patients, PRL, and metabolic parameters (BMI, waist circumference, lipid and glucose profile, insulin, VAI) were assessed at diagnosis and after 12 and 60 months of continuous CAB treatment. MS was evaluated in line with NICE-ATP III criteria.

Results

Compared to baseline, CAB induced a significant decrease in PRL levels after 12 months (P = 0.000) and a further decrease after 60 months (P = 0.000) with complete normalization in 93% of patients. At baseline, MS prevalence was significantly higher in patients with PRL above than in those with PRL lower than the median (187 µg/L) (P = 0.02). MS prevalence significantly decreased after 12 months (12.6%; P = 0.009) and 60% (7% (P = 0.000) months of treatment compared to baseline (32.4%). Total cholesterol and triglycerides were significantly reduced after 12-month CAB compared to baseline (P = 0.03), and further decreased (P = 0.000) after 60-month follow-up. HDL-cholesterol resulted significantly increased after 60-month CAB compared to baseline (P = 0.000) and 12 months of CAB (P = 0.001) and were further improved after long-term CAB (P = 0.03 and P = 0.000 respectively) compared to short-term therapy. Compared to baseline, a slight but not significant decrease in VAI was found at 12-month evaluation, whereas VAI was significantly decreased after 60 months of treatment (P = 0.000).

Conclusions

Short-term CAB treatment significantly improves metabolic profile, so that to reduce MS prevalence, whereas longer treatment is required to achieve a significant improvement of VAI.

DOI: 10.1530/endoabs.32.P866
P868


1Servicio de Endocrinología, Institut Universitari Dexeus, Barcelona, Spain; 2Servicio de Endocrinología, Departamento de Medicina y Centro de Investigación Biomédica en Enfermedades Raras (CIBER-ER Unidad 747), Hospital Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain; 3Servicio de Endocrinología, Complejo Hospitalario Universitario de Santiago de Compostela, Santiago de Compostela, Spain; 4Servicio de Endocrinología, Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain; 5Servicio de Endocrinología, Hospital Universitario Virgen del Rocío, Sevilla, Spain; 6Servicio de Endocrinología, Hospital Universitario La Princesa, Madrid, Spain; 7Servicio de Endocrinología, Hospital Universitario de La Ribera, Valencia, Spain; 8Servicio de Endocrinología, Hospital Universitari San Cecilio, Granada, Spain; 9Servicio de Endocrinología, Hospital Universitario la Paz, Madrid, Spain; 10Servicio de Endocrinología, Hospital Gregorio Marañón, Madrid, Spain; 11Servicio de Endocrinología, Hospital Príncipe de Asturias, Madrid, Spain; 12Servicio de Endocrinología, Hospital La Fe, Valencia, Spain; 13Servicio de Endocrinología, Hospital de Cruces, Baracaldo, Spain; 14Servicio de Endocrinología, Hospital Universitari Germans Trias i Pujol, Barcelona, Spain; 15Servicio de Endocrinología, Hospital Mutua de Terrassa, Barcelona, Spain; 16Servicio de Endocrinología, Hospital de Granollers, Barcelona, Spain; 17Servicio de Endocrinología, Hospital de Bellvitge, Barcelona, Spain.

Pegvisomant (peg) is an effective treatment for acromegaly.

Aim

To investigate the prevalence of escape and the incidence of lipodystrophy with peg treatment.

Methods

Multicenter retrospective study. Escape was defined as loss of control in patients previously controlled under a stable dose of peg, without any other treatment change. Lipodystrophy was defined as either hypertrophy or atrophy of subcutaneous tissue in areas of drug administration.

Results

Ninety-eight patients were included (59% women, mean age at diagnosis 42±13 years, 80% macroadenomas). Ninety-two percent achieved normal IGF-1 on peg. Escape was reported in 33/90 (37%) of responders. Mean time on peg before escape was 22±20 months. The mean initial dose was 11±3 mg/day and mean dose at escape was 14±7 mg/day. Most patients: 30/33 (91%) achieved control with dose increase (57%), medical treatment addition (13%) or both (27%); in one case, escape was temporary. Treatments associated were cabergoline in 50%, somatostatin analogs in 45% and both in 5%. Mean new dose that controlled IGF-1 after escape was 19±8 mg/day. Lipohypertrophy was observed in 14 patients (14.4%) whereas lipoatrophy was observed in one (1%). Lipohypertrophy developed in the abdominal wall in four, arms in two, thighs in four and in multiple sites in four cases and was persistent over time in 30%. Due to lipohypertrophy, peg was discontinued in four patients, four had dose reductions and in six no action was taken. There was no correlation between the presence of escape and lipodystrophy, as well as with multiple clinical variables.

Conclusions

Pegvisomant is an effective treatment for acromegaly, although 37% of responders escaped in long-term follow-up. Most patients achieved control with either dose increase, other medical treatment addition or both. Lipohypertrophy developed in 14% of patients, was persistent in 30% of cases and required drug discontinuation in 28% (four of 14).

DOI: 10.1530/endoabs.32.P868

P869

The effect of the ANKK1/DRD2 Taq1A polymorphism on metabolic side effects of dopamineergic treatment in PRL adenomas

Anastasia P Athanasoulia1, Caroline Sievers1, Manfred Uhr2, Günter Stalla1 & Harald Schneider3

1Department of Internal Medicine, Endocrinology and Clinical Chemistry, Max Planck Institute of Psychiatry, Munich, Germany; 2Department of Pharmacokinetik and CSF Analysis, Max Planck Institute of Psychiatry, Munich, Germany; 3Medizinische Klinik und Poliklinik IV, Ludwig-Maximilians-Universität, Munich, Germany.

Introduction

Treatment with dopamine agonists in patients with PRL adenomas has been associated with weight loss in short-term studies. However, long-term studies on weight changes are lacking. Taq1A is a restriction fragment length polymorphism considered as a gene marker for the DJ2DR gene. The presence of at least one A1 allele is linked to reduced brain dopaminergic activity due to reduced receptor binding and lower density of the dopamine two receptor.

Objectives

We aimed at testing the hypothesis that the dopaminergic treatment in prolactinoma patients leads to sustained weight loss and that the presence of diminished weight loss response under dopamine agonists is associated with the minor A1 allele of Taq1A.

Materials and methods

We included n=44 patients (17 males and 27 females, 26 macroadenomas and 18 microadenomas) with PRL adenomas treated with dopamine agonists (cabergoline, bromocriptine, quinagolide, and metergoline) into this study. Outcome measures were weight and body mass index (BMI) change under dopaminergic treatment after 2 years with regard to Taq1A status.

Results

We observed that the dopaminergic treatment leads to a significant mean weight loss of 3.1±0.25 kg after 2 years. Regarding Taq1A polymorphisms, 21 patients were carriers of at least one A1 allele (genotype A1/A1 or A1/A2) and 23 patients had a genotype of A2/A2. However, the presence of the A1 allele was neither associated with the mean BMI at baseline nor with an altered weight loss response under dopamine agonist therapy.

Discussion

Our results implicate that the dopaminergic treatment leads to a sustained weight loss in patients with PRL adenomas after 2 years. However, there was no association to the A1 allele of Taq1A, observation that needs to be analysed in larger cohorts.

DOI: 10.1530/endoabs.32.P869

P870

Incidental haemorrhage in prolactinomas: is it of any clinical significance?

Komil Sarwar, Bobby Huda, Vanessa Van-de-Velde, Laura Hopkins, Sara Luck, Rebecca Preston, Barbara McGowan, Paul Carroll & Jake Powrie

King’s College London, London, UK.

Background

Incidental pituitary haemorrhage in prolactinomas is a common radiological finding. The clinical significance, associations and outcome of this are largely unknown. Most reports describe surgically treated macroprolactinoma and non-functioning adenoma, and there are few data in a clinic prolactinoma population.

Aims

To characterise the prevalence, natural history and risk factors associated with pituitary haemorrhage in a large clinic prolactinoma population.

Method

A retrospective case-note analysis of 368 patients with prolactinoma attending Guy’s and St. Thomas’ Hospitals between 2000 and 2008. Presence of haemorrhage was noted on magnetic resonance imaging (MRI).

Results

Pituitary haemorrhage was found in 25 patients, giving an overall prevalence of 6.8% which was significantly more prevalent in macroprolactinoma (20.3%) than in microprolactinoma (3.1%) (P<0.0001). Three patients had classical pituitary apoplexy. The majority of patients in the haemorrhage group had macroprolactinoma (16/25 (64%)) and the majority were female (22/25 (88%)). The proportion of females with macroprolactinoma was also higher in the haemorrhage group (14/16 macroprolactinomas (87.5%)) than in the non-haemorrhage group (36/63 macroprolactinomas (57.1%)). P=0.02. The majority of patients were treated conservatively (92%) with 87% of patients having complete resolution of their haemorrhage within 26.6±5.2 (mean±standard
error of mean) months. Anticoagulant therapy, diabetes, hypertension and type of dopamine agonist therapy were not associated with pituitary haemorrhage.

After adjustment for confounders, the presence of macroprolactinoma (odds ratio 9.00 95%CI 3.79–23.88, P < 0.0001) and being female (odds ratio 8.03 (95% CI 1.22–52.95, P = 0.03) were independently associated with haemorrhage.

Conclusion
These data show that haemorrhage is relatively common in macroprolactinoma where one in five develop haemorrhage but is also present in microprolactinoma. The vast majority were clinically silent and resolved spontaneously with only dopamine agonist therapy. We present novel data showing that women, particularly with macroprolactinoma, were more likely to develop haemorrhage in comparison to men.

DOI: 10.1530/endoabs.32.P870

P871
Incidence of pituitary adenomas in Western Sweden in 2001–2011
Kerstin Gunnarsson1, Axel Tjornstrand1, Max Evert1, Erik Holmberg2, Lise-Lott Normann3,1, Thord Rosen1,3, Oskar Ragnarsson1,3 & Helena Filippson Nystrom1
1Institute of Medicine, Sahlgrenska Academy at University of Gothenburg, Göteborg, Sweden; 2Institute of Clinical Sciences, Sahlgrenska Academy at University of Gothenburg, Göteborg, Sweden; 3Department of Endocrinology, Diabetes and Metabolism, Sahlgrenska University Hospital, Göteborg, Sweden.

Background
The number of studies on the incidence of pituitary adenomas (PAs) is limited. The aim of this study was to evaluate the annual incidence of PAs in Västra Götaland, Sweden, with a targeted population of 1.6 million inhabitants.

Patients and methods
Data from adult patients diagnosed with PA in 2001–2011, living in the Västra Götaland County, were collected from the Swedish Pituitary Registry (SPR). In addition, medical records on all patients diagnosed with PA at the six hospitals in the region were reviewed. Those patients who fulfilled a predefined criteria of PA, and had not been registered in the SPR previously, were also included in the analysis. In total, 592 patients were included in the study. Age standardized incidence rate (SIR), given as rate/100 000 inhabitants (95% confidence intervals), was calculated using the WHO 2000 standard population as a reference.

Results
The total SIR for PA during the study period was 3.9/100 000 (3.6–4.3). The SIR in men was 3.3/100 000 (2.9–3.7) and increased with increasing age. In women, the SIR was 4.7/100 000 (4.1–5.3) with the highest incidence in the ages 25–34 years, corresponding to the high frequency of prolactinomas. NFPA was the most common PA (54.1%) with SIR of 1.8/100 000 (1.6–2.0). Prolactinomas were detected in 32% (SIR 1.6/100 000 (1.3–1.9), acromegaly in 9% (SIR 0.35/100 000 (0.25–0.45), Cushing’s disease in 4% (SIR 0.18/100 000 (0.11–0.25) and TSH-producing adenoma in 0.7% (SIR 0.03/100 000 (0.00–0.05)). The frequency of macroadenomas for NFPA, prolactinomas, GH-, ACTH- and TSH-producing adenomas were 82, 37, 77, 28, and 100%, respectively. The life-time risk of PAs in men was 0.27% (0.24–0.31) and in women 0.29% (0.26–0.33).

Conclusion
Hereby, the largest study on the incidence of PAs is presented. The study, conducted during times of frequent use of medical imaging, confirms an increased incidence of PAs compared to older studies.

DOI: 10.1530/endoabs.32.P871

P872
Ursodeoxycholic acid role in chronic cholecystitis progression prevention in acromegaly patients receiving somatostatin analogues
Yuriy Poteshkin, Vyacheslav Pronin, Evgeny Pronin, Evgenia Koltlyarevskaya & Maria Morozova
First MSMU I.M. Sechenov, Moscow, Russia.

Introduction
Acromegaly – a serious debilitating disease resulting in decreased quality and length of life. Due to the late nature of the diagnosis, the lack of prospects for a surgical or non-radical adenomectomy leads to a somatostatin analogues (SA) treatment as primary or secondary therapy, which is a long-term, sometimes lifelong. Therefore, the question of tolerability and prevention of life-threatening complications for these patients is very important. Since the development of gallstones is an expected side effect of long-term use of SA, the authors decided to test the effectiveness of ursodeoxycholic acid (UA) to prevent and cure gallstone patients receiving SA.

Description of methods/design
In a 3-year observation was attended by 44 patients (11 men and 33 women) with acromegaly treated with SA and concomitant chronic cholecystitis. Thirteen patients at baseline revealed gallbladder stones and 31 biliary sludge. Twenty-eight patients received the UA (group 1) and the remaining 16 for various reasons did not receive drug therapy (group 2). Groups did not differ by sex, age (54.2 ± 11.4 and 58.8 ± 8.6), level of IGFBP-1 703 ± 5 ± 369.9 and 676.9 ± 300.8 ng/ml) and GH (3.1 ± 4.4 and 6.1 ± 11.7 ng/ml) and prevalence of cholestasis and biliary sludge. Initial dose was 500 mg UA at night and adjusted every 6 months.

Results
In group 1, none of the patients developed acute cholecystitis, 31% of patients in group 2 developed acute cholecystitis. A negative correlation between UA treatment and acute cholecystitis development in the total group was shown (r = -0.45, P < 0.05). And also noted a negative correlation between the success of therapy and duration of the active phase of acromegaly in patients history (r = -0.89, P < 0.05).

Conclusion
i) Permanent treatment with UA effectively prevent cholecystitis progression in acromegaly patients with SA treatment. ii) Prevention of surgical treatment increase quality of life.

DOI: 10.1530/endoabs.32.P872

P873
Relationship between telomere length and dyslipidemia in patients with Cushing’s syndrome
Anna Aulinas1,2, María José Ramírez3,4, María José Barahona5, Eugenia Mato1,6, Olga Bell1,6, Cristian Valienté3,4, Elena Valassi2,3,2, Eugenia Resmini2,7, Alicia Santos2,7, Iris Crespo2,7, Rosa Corcoyl, Jordi Surralles3,8 & Susan M. Webb1
1Endocrinology Department. Hospital de la Santa Creu i Sant Pau. Universitat Autònoma de Barcelona (UAB), Barcelona, Barcelona, Spain; 2Sant Pau Biomedical Research Institute, Barcelona, Barcelona, Spain; 3Department of Genetics and Microbiology, Universitat Autònoma de Barcelona (UAB), Bellaterra, Barcelona, Spain; 4Center for Biomedical Research on Rare Diseases (CIBERER Unit 745), Valencia, Valencia, Spain; 5Endocrinology Department. Hospital Universitari Mútua de Terrassa, Terrassa, Barcelona, Spain; 6Biomedical Research Networking Center on Bioengineering, Biomaterials and Nanomedicine. CIBER-BBN, Barcelona, Barcelona, Spain; 7Center for Biomedical Research on Rare Diseases (CIBERER Unit 747). Instituto de Salud Carlos III (ICSI11), Barcelona, Barcelona, Spain.

Introduction
Cushing’s syndrome (CS) is associated with increased mortality and morbidities. Hypercortisolism is also present in chronic mood disorders (CMD) and stress, where telomere length (TL) has been found to be shorter than in matched controls. Since hypercortisolism is present in CS and CMD, we hypothesized that telomere shortening could also be present in CS. The aim of this study was to investigate TL in CS patients compared to matched controls.

Methods/design
Transversal study. Thirty-four CS (seven males, 26 pituitary and eight adrenal; six with active disease and 28 cured from hypercortisolism) and 34 matched control patients receiving SA. No patients at baseline revealed gallbladder stones and 31 biliary sludge. Twenty-one CS patients had a greater waist:hip ratio than controls (0.91 ± 0.07 vs 0.89 ± 0.05). No correlation was found with concomitant cortisol values, length of active disease and acute cholecystitis development in the total group was shown (r = -0.45, P < 0.05). And also noted a negative correlation between the success of therapy and duration of the active phase of acromegaly in patients history (r = -0.89, P < 0.05).

Conclusion
In this small group of matched CS/controls, we did not find any differences in TL; however, in CS with dyslipidemia, TL was shortened compared to CS patients with normal lipid values. Further studies will be necessary to confirm this finding and define any possible relationship between hypercortisolism and TL.

DOI: 10.1530/endoabs.32.P873

Endocrine Abstracts (2013) Vol 32

15th European Congress of Endocrinology 2013
Factors Affecting Prognosis in a Series of Acromegalic Patients
Alessandra Fusco1, Antonio Bianchi2, Antonella Giampietro1, Donato Iacovazzo1, Francesca Lugli1, Sabrina Chiloio1, Serena Piacentini1, Linda Tartaglione1, Francesco Doglietto2, Carmelo Anile3, Giulio Maira4 & Laura De Marinis1

1Endocrinology – Catholic University Policlinico A. Gemelli, Rome, Italy; 2Endocrinology – Catholic University Policlinico A. Gemelli, Rome, Italy; 3Neurosurgery – Catholic University Policlinico A. Gemelli, Rome, Italy.

Introduction
The main goal in the treatment of acromegaly is achieving biochemical and tumor mass control. Therapeutic options include surgery, medical treatment and, in selected cases, radiotherapy. A GH receptor (GHR) variant that differs for the genomic retention or exclusion (d3GHR) of exon 3 is present in about 50% of general population and its presence is related to a greater sensitivity to GH.

Materials and methods
We describe a series of 118 patients diagnosed with GH-secreting pituitary adenoma (24 microadenoma, 94 macroadenoma), all submitted to surgery as first-line treatment. All patients with persistent disease after surgery have been treated with somatostatin analogues (SSA) and, among these, non-responder patients have been treated with pegvisomant. We analyzed GH and IGF-1 levels, tumor size and invasiveness, Ki-67 labeling and GHR polymorphism and correlated these findings with prognosis and response to medical treatment.

Results
Twenty-eight/118 patients (23.7%) were considered biochemically cured after surgery; these patients had more frequently microadenomas (35 vs 65%) with lower Ki-67 (1.2 vs 1.7). Among the 90 patients treated with SSA, 64 (71.1%) achieved normal levels of IGF-1 with further ‘escape’ and three patients were compared to d3GHR polymorphism. These three patients presented with higher IGF-1 levels (828 vs 439 ng/ml) and more frequent cavernous sinus involvement (100 vs 77%) compared to controlled ones and they all lacked the d3GHR polymorphism.

Discussion
Our data show that tumor size, local invasiveness and Ki-67 labeling are all prognostic factors in pituitary GH-secreting adenomas. Moreover, lower IGF-1 levels and the presence of the d3GHR polymorphism seem to be correlated with good response to pegvisomant.

DOI: 10.1530/endoabs.32.P874

Metabolic impact of IGF(1CA)19 gene polymorphism on the response to GH therapy in adult GH-deficient (GHD) patients
Claudia Giavoli1,2, Eriselda Profka1,2, Elisa Sala1,2, Marcella Filopanti1,2, Silvia Bergamaschi1,2, Emanuele Ferrante1,2, Maura Arosio1,2, Bruno Ambrosi1,2, Anna Spada1,2 & Paolo Beck-Peccoz1,2

1Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy; 2Endocrinology and Diabetology Unit, Fondazione IRCCS Ca Granda Ospedale Maggiore Policlinico, Milan, Italy; 3Unit of Endocrinology, Ospedale San Giuseppe Multimedica, Milan, Italy; 4Endocrinology and Diabetology Unit, Department of Medical and Surgical Sciences, IRCCS Policlinico San Donato, Donato Milanese, Italy.

A highly polymorphic microsatellite in the IGF-I gene promoter composed of variable cytosine-adenine (CA) repeats (n = 10–24) has been linked to IGF-I levels, risk of diabetes and cardiovascular diseases with conflicting results. Aim of this study was to investigate the impact of this polymorphism on the response to rhGH (mean dose 0.34 ± 0.14 mg/day) in adult GH-deficient (GHD) patients after 1 (n = 98) and 5 (n = 50) years. Different genotypes were studied by microsatellite method, according to the most frequent 192 bp allele (19 CA repeats) subjects were divided into three groups: homozygous (192/192, n = 38), heterozygous (192X, n = 44) and non-carriers (XX, n = 16). Allelic distribution was similar in the subgroup followed for 5 years. The genotype did not influence neither the phenotype of patients at baseline (including IGF-I levels), nor their response to rhGH in terms of decrease in BF% and increase in IGF-I levels. Conversely, after 1 year, there was a significant worsening of insulin sensitivity, documented by increase in fasting glucose levels and HOMA-IR (from 81 ± 8 to 86 ± 8 mg/dl and from 1.7 ± 1.0 to 2.4 ± 1.6 respectively, P < 0.001), as well as a significant improvement in lipid profile shown by reduction in total and LDL-cholesterol (from 215 ± 42 to 192 ± 39 and from 138 ± 38 to 111 ± 34 mg/dl respectively, P < 0.001) only in homozygous. During long-term treatment, HOMA-IR restored to basal values in all patients, though fasting glucose levels remained higher than at baseline in homozygous. The decrease in total and LDL-cholesterol was significant both in homozygous and in heterozygous, but not in non-carriers. No difference among groups was observed in rhGH dose throughout study. In conclusion, the presence of the wild-type allele in the IGF-I gene promoter might increase sensitivity to metabolic changes induced by rhGH, either negative or positive. In the long-term, beneficial effects (i.e. persistent BF% reduction) may overcome the negative impact on glucose metabolism regardless IGF-I genotype, while positive effects on lipid profile manifest in patients carrying at least one 192 allele.

DOI: 10.1530/endoabs.32.P876

Hyponatremia (serum sodium <135 mmol/l), the most common electrolyte disorder encountered, has been associated with increased mortality in patients with particularly cancer, heart failure, chronic kidney and liver disease. However, evidence of the clinical implications in broader populations is scarce, and uncertain due to confounding from preexisting disease. We aimed to examine the association between admission-hyponatremia and 30-day mortality in acute non-surgical patients.

Introduction
A 15th European Congress of Endocrinology 2013

Vol 32

Endocrine Abstracts (2013) Vol 32

Discussion
Admission-hyponatremia was associated with increased risk of death for all levels of hyponatremia, even after adjusting for higher comorbidity level in hyponatremic patients. The risk increased with decreasing sodium levels.

DOI: 10.1530/endoabs.32.P875

Thirty-day mortality in acute non-surgical patients admitted with hyponatremia
Louise Holland-Bill1, Christian Christiansen1, Troels Ring2, Henrik Toft Sorensen1 & Jens Otto Lunde Jorgensen1

1Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; 2Department of Nephrology, Aalborg University Hospital, Aalborg, Denmark; 3Department of Endocrinology, Aarhus University Hospital, Aarhus, Denmark.

Introduction
Hyponatremia (serum sodium ≤135 mmol/l), the most common electrolyte disorder encountered, has been associated with increased mortality in patients with particularly cancer, heart failure, chronic kidney and liver disease. However, evidence of the clinical implications in broader populations is scarce, and uncertain due to confounding from preexisting disease. We aimed to examine the association between admission-hyponatremia and 30-day mortality in acute non-surgical patients.

Method
We conducted a population-based cohort study in North and Central Denmark Regions, comprising approximately 1.8 million inhabitants. We identified all patients acutely admitted to non-surgical departments from January 1, 2000 to December 31, 2000, for whom serum sodium was measured on the day of admission using individual level linkage of the Danish National Patients Registry, the Danish Civil Registration System and the Clinical Laboratory Information System. Admission-hyponatremia was categorized as mild (130–135 mmol/l), moderate (125–129.9 mmol/l) and severe (<125 mmol/l). Thirty-day mortality for normonatremia and levels of admission-hyponatremia were estimated using the Kaplan–Meier method. Mortality rate ratios (MRRs) were estimated using a Cox regression model, adjusting for sex, age and comorbidity level.

Results
We identified 302,311 acute non-surgical patients, with a sodium measurement on the first day of admission. Admission-hyponatremia was present in 70,410 patients (prevalence=23%). Hyponatremic patients were older and had higher comorbidity levels than normonatremic patients. Cumulative 30-day mortality for patients with admission-hyponatremia was 8.8% compared with 3.9% in normonatremic patients. Mortality was increased throughout the period. Adjusted MRR was 1.78 (95% CI: 1.72–1.84) for any hyponatremia compared with normonatremia. Adjusted MRR for mild, moderate and severe hyponatremia compared with normonatremia was 1.59 (95% CI: 1.54–1.65), 2.32 (95% CI: 2.19–2.46) and 2.40 (95% CI: 2.23–2.60) respectively.

Discussion
Admission-hyponatremia was associated with increased risk of death for all levels of hyponatremia, even after adjusting for higher comorbidity level in hyponatremic patients. The risk increased with decreasing sodium levels.

DOI: 10.1530/endoabs.32.P876
P877
Hypopituitarism after fractionated stereotactic radiation therapy of anterior skull base meningiomas is caused by mass effects, not radiation
Emil Moeller, Arnar Astradsson, Marianne Klose, Henrik Roed, Ulla Feldt-Rasmussen & Marianne Juhler
Rigshospitalet, Copenhagen, Denmark.

Introduction
Fractionated stereotactic radiotherapy (FSRT) is used in the treatment of surgically inaccessible meningiomas, primarily in the base of the skull. Development of hypopituitarism following FSRT is inexactastically investigated. We aimed to elucidate the cause of hypopituitarism in patients treated with FSRT for benign meningiomas of the anterior skull base.

Methods
All patients undergoing FSRT for benign meningioma of the skull base between July 2003 and June 2009 were included in the study. Patients baseline was established before FSRT and they were then followed with regular neuroendocrinological testing. Tumour control was monitored at neurosurgical follow-up every 2 years using MRI. Pituitary radiation dose was calculated using the dose-volume histogram for the pituitary gland generated by the radiation planning program.

Results
A 31 patients were included in the study. Median follow up was 5.2 years (range 2.2–7.8). Ten patients developed one or more new pituitary hormone deficits. Five years after FSRT, 70–79% of patients retained sufficient hormone function in each axis included in the study. Tumour control (defined as either a stable or regressing tumour) was obtained in 81% of cases. Median biological effective dose to the pituitary gland was 83 Gy (range 32–92). Multiple linear regression analysis showed that there was a statistically significant relationship between i) failure of tumour control ($P=0.0005$), ii) tumour in the pituitary sella ($P<0.0001$) and iii) time from FSRT to latest follow-up ($P=0.0116$) and the number of affected pituitary axes.

Conclusion
Our results show a significant relationship between mass effects of the tumour and pituitary axis failure as well as a significant time component in the development of hypopituitarism in these patients. It is possible that the findings of this study can explain pituitary axis failure in patients treated with radiation therapy for pituitary adenoma and craniopharyngioma.

DOI: 10.1530/endoabs.32.P877

P878
Role of IGF(CA)19 gene polymorphism in the clinical presentation of acromegaly
Elisa Sala, Giovanna Mantovani, Emanuele Ferrante, Anna Maria Barbieri, Elena Malchiodi, Elisa Verrua, Claudia Giavoli, Marcello Filopanti, Paolo Beck-Peccoz & Anna Spada
Department of Clinical Sciences and Community Health, Endocrinology and Diabetology Unit, University of Milan, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy.

Introduction
A highly polymorphic microsatellite, comprising a variable length of a cytosine–adenosine (CA) repeat sequence, has been identified in the promoter region of IGF-I gene. The number of CA repeats ranges between 10 and 24 and the most common allele in the Caucasian population contains 19 CA (192 bp) repeats. A highly polymorphic microsatellite, comprising a variable length of a cytosine–adenosine (CA) repeat sequence, has been identified in the promoter region of IGF-I gene. The number of CA repeats ranges between 10 and 24 and the most common allele in the Caucasian population contains 19 CA (192 bp) repeats.

Materials and methods
Differrent genotypes were studied by microsatellite method and patients were divided into three groups: group A, homozgyous for 192 bp allele ($n=26$, 29.2%); group B, with a number of repeats $\geq 19$ ($n=36$, 40%) and group C, with a number of repeats $\leq 19$ ($n=27$, 30%). Ninety-eight healthy patients were analyzed as controls.

Results
No difference in the frequency of the different alleles was observed between patients and controls. In the acromegalic population, the genotype did not influence IGF-I level at diagnosis. However, a worse of insulin sensitivity documented by a significant increase ($P=0.01$) in HOMA-IR was observed in group B ($6.2 \pm 5.9$) compared with group A ($5.0 \pm 3.3$) and C ($4.0 \pm 3.1$). Moreover, higher levels of total cholesterol and LDL ($P=0.01$ and $P=0.01$ respectively) were present in group B ($233 \pm 49$ and $168.5 \pm 46.6$ respectively) compared to group C ($175.3 \pm 43.4$ and $104.0 \pm 38.2$ respectively). Interestingly, the number of discrepant patients (high IGF-I and normal GH levels) during medical therapy was significantly higher in group B compared to groups A ($P=0.02$) and C ($P=0.05$).

Conclusion
Different IGF-I genotypes do not account for a different presentation in acromegalic patients. Nevertheless, our data suggest that a number of CA repeat higher than 19 may be related to a worse glaucidic and lipidic metabolism and to a partial disease control during medical treatment.

DOI: 10.1530/endoabs.32.P878

P879
Relationship between early endocrine alterations and functional outcome in patients with severe brain injury
Djordje Marina1, Marianne Klose1, Annette Nordenskke1,2, Annette Liebach1,2, Lars Westergaard1,2 & Ulla Feldt-Rasmussen1
1Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; 2Hvidovre Hospital, Copenhagen University Hospital, Copenhagen, Denmark.

Introduction
Recently, it has been suggested that hypopituitarism developed after the brain injury has implications in the final recovery of the patients. We hypothesize that hypopituitarism developed in the course of traumatic brain injury (TBI) or non-TBI is related to worse functional outcome. The aim was to assess the association between hypopituitarism in the early recovery phase and long-term functional outcome.

Materials and methods
We included 157 brain-injured patients (107 TBI; 50 non-TBI) referred to the Department of Neurorehabilitation, Hvidovre Hospital from 06/2007–05/2011. Pituitary assessment including a 250 μg Synacthen® test was performed 3.5 (±1.5) months post-injury. Insufficiencies were defined as pituitary and peripheral hormone concentrations in relation to local gender and age-related reference ranges. Functional outcome was assessed by Glasgow outcome scale extended (GOS-E), functional independence measure (FIM), and Rancho Los Amigos scale at 1-year follow-up.

Results
Hormone alterations were observed in 72.5% of the patients. Hyperprolactinaemia, secondary hypogonadism, and hypothyroidism were recorded in 50, 21, and 9% of TBI patients and in 48, 22, and 17% of non-TBI patients, respectively. Adrenal insufficiency was recorded in one non-TBI patient. Presence of secondary insufficiencies was unrelated to aetiology, shearing lesions, time since injury and antiepileptic drug treatment. Hyperprolactinaemia was related to better neurorehabilitation, while hypothyroidism was related to worse outcome at 1 year follow-up, as measured by FIM ($P<0.03$) and GOS-E ($P<0.01$). In non-TBI patients no such relations were demonstrated.

Conclusion
A substantial number of severely brain-injured patients had hormonal alterations approximately 3-months post-injury. In the TBI group, hyperprolactinaemia and secondary hypogonadism was related to poorer outcome. The importance of the observed alterations for the rehabilitation process, and the long-term consequences, however, remain to be proven.

DOI: 10.1530/endoabs.32.P879
P880
Limitations of basal IGF-I status reflecting the severity of growth hormone deficiency and predicting response to replacement therapy
A retrospective cohort study in a tertiary referral centre in Spain
Laura Perez, P. Pizarra, Alberto Fernandez, Maria Augusta Guillen, Luis Felipe Pallardo & Cristina Alvarez
Hospital La Paz, Madrid, Spain.

GH replacement (GHR) in adults has demonstrated to improve body composition, inflammatory cardiovascular biomarkers and quality of life. However, this benefit is uneven, and factors that stratify treatment response are required.

According to current guidelines, low IGF-I levels in specific conditions provide strong evidence for GH deficiency (GHD). Nevertheless, normal levels do not exclude this diagnosis and make mandatory the use of GH stimulation testing. It has not been described before if GH deficient patients with normal IGF-I get the same clinical benefit from replacement as individuals with low IGF-I.

The aim of this study is to compare the response to GHR between the subgroup with normal IGF-I and patients with low IGF-I.

We analyzed retrospectively 34 GHD adults (mean age 40.4 years; 16 females) from our centre who received GHR for at least 2 years (mean duration of treatment 7.4 years). Anthropometric parameters, bone mineral density (BMD) of the lumbar spine and hip, and the scores in quality of life questionnaires (AGHDA and Nottingham) were measured before starting treatment and at the end of the follow-up. Differences in these parameters were tested by Mann-Whitney U test.

No significant differences were found in the baseline parameters between the subgroup with normal IGF-I and patients with low IGF-I. The AGHDA and Nottingham mean scores improved significantly at the end of follow-up (~3 to 3.95; P=0.003 and ~3.8 to 7.4; P=0.01 respectively) but there were no differences between patients with normal or low IGF-I (P<0.19 and P<0.533). No significant changes were observed in BMD or body composition.

Our data show that benefits of GHR are maintained across different scales of IGF-I secretion. Thus, this study highlights the limitations of basal IGF-I status in reflecting the physiopathology of GHD, indicating the severity of GHD and selecting candidates for replacement.

DOI: 10.1530/endoabs.32.P880

P881
Effects of gender and body composition on GH response to GHRH + Arg in HIV- lipodystrophic patients: higher rate of GH deficiency in men
Giulia Braginti1,2, Chiara Dizzai1,2, Giulia Ferrannini1,2, Anna Ansalone1,2, Lucia Zirilli1,2, Giovanni Guarnaldi2 & Vincenzo Rochira1,2,3
1Chair and Unit of Endocrinology and Metabolism, Department of Biomedical, Metabolic and Neuronal Sciences, University of Modena and Reggio Emilia, Modena, Italy; 2Integrated Department of Medicine, Endocrinology and Metabolism, Geriatrics, Azienda USL of Modena, NOCSAE of Baggiovara, Modena, Italy; 3Medizinische Klinik und Poliklinik IV, Universita¨t M u¨ nchen, Munich, Germany.

Introduction
Sub-Pituitary Clinical (Generously supported by IPSEN) is still unclear whether obesity in craniohypogonadism (CP) is caused by disorders in food regulation or by changes in mood or activity due to depression or sleepiness leading to a decrease in energy consumption. We compared CP patients to non-functioning pituitary adenoma (NFPA) by using standardized questionnaires to clarify this question.

Methods
We compared 31 CP (m = 14, f = 17, median age: 53 years (26–77)) to 26 NFPA (m = 19, f = 7, median age: 65 years (44–80)). Patients were asked to complete eleven standardized German questionnaires. Two questionnaires evaluated eating disorders (FEV, Eating-Disorder-Examination-Questionnaire), one depression (BDI, Beck-Depression-Inventory), one anxiety (STAI, State-Trait Anxiety Inventory), three health-related quality of life (SF-36, EuroQoL, Qol-AHGDA), two sleepiness (Epworth Sleepiness Scale), two personality (EQP-RK, Eysenck Personality Questionnaire-Revised; TPQ, Tridimensional Personality Questionnaire) and one body image (FBK-20).

Results
Both groups had the same prevalence of hormonal insufficiencies of the anterior pituitary. Patients with CP scored significantly higher in concious hunger perception (FEV, CP 6 scores (1–12), NFPA 2 scores (0–11), P=0.016) and in the Eating-Disorder-Examination-Questionnaire (CP 1.7 scores (0.1–3.7), NFPA 0.8 scores (0–4.4), P=0.039). In the latter the score for the subscale eating concern were higher compared to NFPA (CP 2 scores (0–5), NFPA 0.8 scores (0–6), P=0.04). Furthermore, they had higher scores in anxiety (STAI, CP 39 scores (23–60), NFPA 32 scores (23–62), P=0.052) and disturbed eating behaviour (FEV, CP 5 scores (0–12), NFPA 3 scores (0–13), P=0.064), but without reaching statistical significance. No differences could be seen in depression, personality, quality of life or sleepiness.

Conclusion
CP score higher in questionnaires of eating disorders than NFPA but not in questionnaires concerning mood or activity. Therefore, obesity in CP appears to be a consequence of eating disorders.

*This work was partly, financially supported by Ipsen GmbH.

DOI: 10.1530/endoabs.32.P881

P882
Obesity in patients with craniohypogonadism seems to be caused by eating disorders rather than changes in mood or activity
Joseline Roemmler1, Veronika Appelweg1, Cristina Dimopoulou1,2, Caroline Sievers2, Guenther Stall3 & Jochen Schopohl1
1Medizinische Klinik und Poliklinik IV, Universita¨t M u¨ nchen, Munich, Germany; 2Max-Planck-Institut, Department for Endokrinologie, Munich, Germany.

Background
SUB-Pituitary Clinical (Generously supported by IPSEN) is still unclear whether obesity in craniohypogonadism (CP) is caused by disorders in food regulation or by changes in mood or activity due to depression or sleepiness leading to a decrease in energy consumption. We compared CP patients to non-functioning pituitary adenoma (NFPA) by using standardized questionnaires to clarify this question.

Methods
We compared 31 CP (m = 14, f = 17, median age: 53 years (26–77)) to 26 NFPA (m = 19, f = 7, median age: 65 years (44–80)). Patients were asked to complete eleven standardized German questionnaires. Two questionnaires evaluated eating disorders (FEV, Eating-Disorder-Examination-Questionnaire), one depression (BDI, Beck-Depression-Inventory), one anxiety (STAI, State-Trait Anxiety Inventory), three health-related quality of life (SF-36, EuroQoL, Qol-AHGDA), two sleepiness (Epworth Sleepiness Scale), two personality (EQP-RK, Eysenck Personality Questionnaire-Revised; TPQ, Tridimensional Personality Questionnaire) and one body image (FBK-20).

Results
Both groups had the same prevalence of hormonal insufficiencies of the anterior pituitary. Patients with CP scored significantly higher in concious hunger perception (FEV, CP 6 scores (1–12), NFPA 2 scores (0–11), P=0.016) and in the Eating-Disorder-Examination-Questionnaire (CP 1.7 scores (0.1–3.7), NFPA 0.8 scores (0–4.4), P=0.039). In the latter the score for the subscale eating concern were higher compared to NFPA (CP 2 scores (0–5), NFPA 0.8 scores (0–6), P=0.04). Furthermore, they had higher scores in anxiety (STAI, CP 39 scores (23–60), NFPA 32 scores (23–62), P=0.052) and disturbed eating behaviour (FEV, CP 5 scores (0–12), NFPA 3 scores (0–13), P=0.064), but without reaching statistical significance. No differences could be seen in depression, personality, quality of life or sleepiness.

Conclusion
CP score higher in questionnaires of eating disorders than NFPA but not in questionnaires concerning mood or activity. Therefore, obesity in CP appears to be a consequence of eating disorders.

*This work was partly, financially supported by Ipsen GmbH.

DOI: 10.1530/endoabs.32.P882

P883
Correlation of clinical smell test and magnetic resonance imaging of olfactory system in idiopathic hypogonadotropic hypogonadism
Sunil Kumar Kota1, Lalit Kumar Meher1, Sruiti Jammula1 & Kiritkumar D Modi2
1Medwin Hospital, Hyderabad, Andhrapradesh, India; 2MKCG Medical College, Berhampur, Orissa, India.

Objectives
i) To measure olfactory bulbs and sulci using dedicated magnetic resonance imaging (MRI) sequences in idiopathic isolated hypogonadotropic hypogonadism (IHH) patients with a well detailed phenotype characterization. ii) To correlate MRI findings with a clinical smell test.
Methods
SUB: Pituitary – Clinical (Generously supported by IPSEN/MRI was performed in 20 patients (all males, aged between 11 and 45 years, mean age of 26) with IH and olfactory dysfunction was assessed using the smell identification test (UPSIT), a qualitative suprathreshold olfaction test obtained from the Universtitat Pennsylvania. Coronal spin echo T2-weighted and volumetric T1-weighted gradient echo sequences were acquired in a 1.5T system. Imaged software was used to obtain olfactory bulb volumes and olfactory sulcus depths and lengths. Data were analyzed with SPSS 13.0 and the Kappa index was used to evaluate the agreement between the UPSIT and MRI.

Results
The UPSIT revealed normosmia, hyposmia and anosmia in 10 (50%), 4 (20%) and 6 (30%) patients respectively. Fourteen patients (70%) had olfactory abnormalities in the MRI. Commonest abnormality was hypoplasia seen in 8 patients (40%). Five patients (25%) had olfactory bulb. One patient had unilateral hypoplasia with normal sense of smell. There was moderate agreement between the MRI quantitative evaluation and the UPSIT (overall Kappa = 0.55).

Discussion
Olfactory bulb and sulcus aplasia were the most common findings in IH patients (70%). We objectively demonstrated agreement between MRI findings and the smell test, especially the presence of bulb aplasia and anosmia, confirming the high specificity of MRI findings.

Conclusion
Therefore, our findings help ascertain MRI accuracy in the diagnosis of IHH, differentiating patients with hypogonadotropic hypogonadism with an apparently normal or difficult to evaluate sense of smell.

DOI: 10.1530/endobs.32.P883

P884
Diencephalic syndrome before diagnosis of childhood craniopharyngioma: results of multinational studies on 485 long-term survivors after childhood craniopharyngioma
Anika Hoffmann1, Anthe Sterkenburg2,3, Ursel Gebhardt1 & Hermann Müller1
1Department of Pediatrics, Klinikum Oldenburg, Oldenburg, Germany; 2University Hospital Groningen (UMCG), Groninghe, The Netherlands.

Background
SUB: Pituitary – Clinical (Generously supported by IPSEN/Hypothalamic involvement (HI) resulting in severe obesity is known to have major impact on quality of life in craniopharyngioma (CP) patients. HI is also associated with disturbances of satiety regulation leading to a failure to thrive and weight loss known as diencephalic syndrome (DS). The rate of DS and the outcome of CP patients with DS is unknown.

Methods
CP patients have been recruited in HIT-ENDO and KRANIOPHARYNGEOM 2000/2007. 21 CP patients (4.3%) presented with a BMI < 2 s.d. at diagnosis. In 4 of 21 cases low BMI could be explained by prematurity or congenital heart failure. Eleven patients presented with DS due to proven hypothalamic involvement (HI). Three patients presented without HI, in three patients HI was not evaluable. We compared weight development since birth at standardized time points (based on a German health survey) in CP presenting DS, normal weight or obesity (BMI > 3 s.d.) at the time of diagnosis.

Results
Weight development during early childhood could be analyzed in 9 of 11 DS patients. Decreases in BMI (> - 1 s.d.) were detectable in 4 patients within the first year of life, in two patients in the second year of life, in two patients in the 5th year, one patient was already dystrophic at birth. Accordingly, 7 of 11 patients showed BMI reduction within the first two years of life. During follow-up, DS patients showed a significant postoperative weight gain comparable to patients who presented with normal weight at time of diagnosis resulting in obesity (median BMI + 3.98 s.d.) after 8–12 years.

Conclusion
DS is a rare clinical manifestation of CP. In the majority BMI SDS reduction becomes manifest in early childhood, in some cases changes in BMI SDS develop later, but years before other symptoms are obvious. Low BMI at time of diagnosis does not prevent weight gain in CP with DS.

DOI: 10.1530/endobs.32.P884

P885
Xanthogranuloma, Rathke's cyst, and Childhood Craniopharyngioma: results of prospective multinational studies of children and adolescents with rare sellar malformations
Hermann Müller1, Ursel Gebhardt1, Andreas Feldum2, Monika Warmuth-Metz2, Torsten Pietsch2, Fabian Pohl1, Gabriele Calaminus8 & Niels Sörensen1
1Department of Pediatrics, Klinikum Oldenburg, Oldenburg, Germany; 2Institute of Biostatistics and Clinical Research, Westphälische Wilhelms University, Münster, Germany; 3Department of Neuroradiology, University Hospital, Würzburg, Germany; 4Institute of Neuropathology, University Hospital, Bonn, Germany; 5Department of Radiooncology, University Hospital, Regensburg, Germany; 6Department of Pediatric Oncology, Münster, Germany; 7Department of Neurosurgery, Evangelisches Krankenhaus, Oldenburg, Germany.

Background
SUB: Pituitary – Clinical (Generously supported by IPSEN/Craniopharyngioma (CP), Rathke’s cyst (RC) and xanthogranuloma (XG) are closely related rare sellar masses, which share common embryogenic origin. Treatment strategies in children lack consensus, especially in terms of surgical and radiooncological treatment options.

Objective
To study clinical manifestations and treatment-related outcome in CP, XG, and RC patients.

Patients and methods
Multicentre surveillance trial. Inclusion criteria were: i) histological diagnosis of CP, XG, or RC; ii) diagnosis: Main Outcome: overall survival, event-free survival (OS, EFS), quality of life (QoL). 14 RC, 14 XG, and 117 CP patients were included in the study.

Results
Five-Year OS rates are 1.00 ± 0.00 in RC and XG; 0.97 ± 0.02 in CP. 5-year EFS are 0.85 ± 0.10 in RC, 1.00 ± 0.00 in XG, and 0.50 ± 0.05 in CP. Surgical resection of XG results in complete remission without recurrence. Recurrences occur in RC (14%) and CR (59%), but can be efficiently treated by irradiation, reoperation, and/or intracystic treatment. Severe hypothalamic sequelae such as obesity and others affecting QoL are predominant in CP due to pre-surgical involvement (59%) and post-surgical lesions (44%) of posterior hypothalamic structures. Centres with lower neurosurgery patient load use more radical surgical approaches to treat CP, resulting in higher rates of obesity and reduced QoL. In spite of 46% anterior hypothalamic involvement, severe obesity is not encountered in XG.

Conclusions
Treatment of choice in XG and RC is radical surgery. In CP involving hypothalamic structures, less radical surgical approaches preserving hypothalamic integrity are recommended. Owing to frequent relapses, regular imaging during follow-up is recommended for CP and RC. Treatment of patients with sellar masses should be confined to experienced multidisciplinary teams. Due to the rareness of the diseases, international scientific collaboration (i.e. international trials) is recommended in order to achieve reliable results based on evaluation of larger cohorts.

DOI: 10.1530/endobs.32.P885

P886
Short-term exercise-induced GH response in athletes: differential results for runners and bikers when tested on bicycle
Thomas Zueger, Julie Bucher, Emanuel Christ & Christoph Stettler
Division of Endocrinology, Diabetes & Clinical Nutrition, University Hospital and University of Bern, Bern, Switzerland.

Background/introduction
SUB: Pituitary – Clinical (Generously supported by IPSEN/We have previously shown that GH assessment during a standardized aerobic exercise of moderate intensity is a reliable test with high diagnostic accuracy in predicting severe GH deficiency (GHD) in adult individuals. However, these studies comprised comparatively long exercise durations around 60 min or longer. To improve clinical applicability of exercise testing in the diagnosis of GHD a shorter test protocol would be preferable. The present study investigated the exercise-induced GH response in healthy athletes during a stepwise incremental VO2 peak testing on a bicycle. We hypothesized that GH response would be smaller in bikers investigated on the bicycle compared with their running counterparts.

Methods
Nine endurance trained athletes volunteered to participate to this part of the study (seven males and two females), mean ± s.d. age was 33 ± 9.7 years. Participants were randomly assigned to perform a standardized exercise protocol on both a running treadmill and on a bicycle ergometer. The running test started at a speed of 8 km/h and increased by 1 km/h every 2 min. The running test started at a speed of 8 km/h and increased by 1 km/h every 2 min. Decline in speed was made at 20 min. Total duration of the running test was 32 min. The bicycle test started at a load of 20 W and increased the load every 3 min. Load was increased by 10 W every 3 min. Target HR was 85% of maximum HR. Load was increased at 30 min. Total duration of the bicycle test was 35 min.

Results
The GH response during both running and bicycle tests was significantly correlated with the VO2 peak, with the GH response being greater for the running test. The GH response during the running test was significantly greater than during the bicycle test. Additionally, the GH response during the running test was significantly greater than during the bicycle test for both VO2 peak and VO2 reserve.

Conclusions
The results of the present study suggest that the exercise-induced GH response is differentially affected by exercise mode and that the running test is a more sensitive test for the diagnosis of GHD than the bicycle test.

DOI: 10.1530/endobs.32.P886
were divided into two subgroups according to their prevalent exercise habits (bikers or runners). VO2 peak testing was performed fasting in the morning on an electrically braked bicycle with gradually increased workload until exhaustion. Blood samples for GH were taken immediately before and after exercise, as well as at 15, 30, and 45 min after end of exercise. After testing for normal distribution GH values were compared by t-test.

Results

The mean±s.d. exercise duration was 11.0±1.5 min. Mean VO2 peak was 54.6±5.83 ml/kg. For athletes mainly exercising on bike mean GH values were 1.97±1.9, 2.29±1.8, 3.33±3.0, 2.23±1.9 and 1.72±1.4 ng/ml before, directly after exercise and at 15, 30, and 45 min after the test respectively. The corresponding GH values in athletes whose exercise mainly consisted of running were 2.51±3.3, 8.48±7.9, 12.50±7.5, 10.90±6.6, and 9.82±8.7 ng/ml. Peak GH was significantly lower in bikers compared with runners (3.59 vs 54.6 ng/ml). Exercise testing induced a strong GH response in both groups, but the GH secretion was lower in bikers compared with runners. This difference may be due to habituation effects resulting in a weaker stimulus.

Conclusion

Based on these preliminary results in athletes a short stepwise exercise test increasing to exhaustion appears a promising test opportunity to provoke pituitary GH secretion under standardized conditions. However, when investigating individuals performing regular exercise the type of activity may be of importance in the choice of the test conditions. While bicycle testing induced a strong GH response in runners it resulted in considerably lower GH stimulation in bikers. This difference may be due to habituation effects resulting in a weaker stimulus. Whether testing bikers on a treadmill will revert this effect will have to be studied in a next step. Furthermore, we will now investigate short-term exercise induced GH response in GH deficient patient as well as in matched but sedentary controls.

DOI: 10.1530/endoabs.32.P886

---

**P887**

**Gender determines ACTH recovery after experimental hypercortisolemia in older individuals**

Animesh Sharma1, Paul Aoun1,2, Jean Wigham1, Sue Weist1 & Johannes Veldhuis1

1Mayo Clinic, Rochester, Minnesota, USA; 2Palm Beach Diabetes and Endocrine Specialists, West Palm Beach, Florida, USA.

Introduction

Available clinical literature raises the possibility that stress-responsive mechanisms differ by gender, especially in older individuals; however the accompanying evidence is both limited and discrepant. We hypothesize that gender determines the degree of ACTH inhibition by and recovery after an experimental cortisol clamp in older subjects. Subjects and design

We conducted a prospectively randomized, double-blind, placebo-controlled, crossover study in 10 older men and 10 post-menopausal women (age group 50–80 years) in the clinical research unit of a tertiary medical center. Methods

Volunteers received oral placebo or ketoconazole (KTCZ), to inhibit adrenal steroidogenesis, along with 8 h.i.v. infusions of saline or a low (2.5 mg/m2) vs. high (10 mg/m2) physiological dose of i.v. cortisol. ACTH and cortisol concentrations were measured every 10 min during the last 4 h of the saline and cortisol infusions (feedback-clamp phase) and for 10 h thereafter (recovery phase). Primary outcomes measure

Plasma ACTH concentrations. Results

Gender did not determine mean ACTH concentrations during the feedback-clamp phase of saline or cortisol infusions. However, compared with men, women had markedly impaired mean (and peak) ACTH recovery from experimental cortisol infusion (P = 0.005, KTCZ/low-dose cortisol arm; P = 0.006, KTCZ/high-dose cortisol arm). Non-linear regression of ACTH on time confirmed attenuated ACTH recovery in women. Decreased ACTH recovery was accompanied by lower mean cortisol concentrations, pointing to attenuated feedforward drive of ACTH secretion rather than reduced cortisol clearance as the sex-related mechanism.

Conclusion

Gender determines the recovery of the hypothalamic–pituitary–ACTH unit from cortisol-induced feedback, with attenuated responses in post-menopausal women. The gender differences may have relevance to stress-related adaptations in the sexes.

DOI: 10.1530/endoabs.32.P887

---

**P888**

**Levels of prolactin, FSH and LH pool vs single sample determination**

Sandra Belo1,2, Selma Souto1,2, Angela Magalhães1,2, Davide Carvalho1,2 & João Tiago Guimarães1

1Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar de São João, Porto, Portugal; 2Faculty of Medicine, University of Porto, Porto, Portugal.

Introduction

The assessment of pituitary function is often achieved by means of sequential determinations (pool) of hormone levels such as prolactin and gonadotrophins. For the determination of prolactin levels the guidelines of the Endocrine Society are clear in recommending a single sample determination.

Objective

To evaluate differences between single sample and pool (0’, 20’ and 60’) determinations for assessing prolactin, FSH and LH levels.

Methods

We conducted a cross-sectional study including 4610 prolactin pools, 2628 FSH pools and 2568 LH pools performed between 2009 and 2011. Statistical analysis was performed using the paired samples t-test.

Results

We found differences between prolactin levels in determinations at 0’, 20’ and 60’ (21.5±64.6 vs 20.0±63.9 ng/ml, P < 0.001). The mean difference between prolactin levels at 0’ and 20’ was 1.8±7.6 ng/ml at 0’ and 60’ 2.8±8.6 ng/ml and at 20’ and 60’ 1.0±7.1 ng/ml. Regarding FSH pools there were also found differences in hormone levels between determinations at 0’, 20’ and 60’ and between the FSH level at 0’ and the mean of the three determinations (21.5±64.6 vs 20.0±63.9 ng/ml, P < 0.001). The mean difference between prolactin levels at 0’ and 20’ was 1.8±7.6 ng/ml at 0’ and 60’ 2.8±8.6 ng/ml and at 20’ and 60’ 1.0±7.1 ng/ml. Regarding FSH pools there were also found differences in hormone levels between determinations at 0’, 20’ and 60’ and between the FSH level at 0’ and the mean of the three determinations (20.9±27.3 vs 20.1±20.4 vs 10.0±26.3 mlU/ml, P < 0.001; 20.9±27.3 vs 20.3±26.6 mlU/ml, P < 0.001), and the same was observed for LH pools (11.9±12.8 vs 11.4±12.3 vs 11.0±12.1 mlU/ml, P < 0.001; 11.9±12.8 vs 11.4±12.3 vs 11.0±12.1 mlU/ml, P < 0.001). The mean difference between the FSH levels at 0’ and 20’ was 0.7±2.3 mlU/ml, at 0’ and 60’ 0.9±2.3 mlU/ml and at 20’ and 60’ 0.1±1.9 mlU/ml when considering LH pools the results were 0.5±2.2, 1.2±2.5, and 0.4±1.8 mlU/ml.

Conclusion

Despite the presence of differences in hormone levels between pool determinations these differences, given its range, do not appear to have clinical significance.

DOI: 10.1530/endoabs.32.P888

---

**P889**

**Tumors with simultaneous hypersecretion of somatotropin and prolactin are associated with earlier diagnosis compared with tumors with isolated hypersecretion of somatotropin**

Sandra Belo1,2, Cláudia Nogueira1,3, Angela Magalhães1,2, Eduardo Vinha1, Joás Pereira2 & Davide Carvalho1,3

1Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar de São João, Porto, Portugal; 2Department of Neurosurgery, Centro Hospitalar de São João, Porto, Portugal; 3Faculty of Medicine, University of Porto, Porto, Portugal.

Introduction

Amenorrhoea and galactorrhoea are manifestations that may allow earlier diagnosis of pituitary tumors with isolated hypersecretion of somatotropin. Despite the presence of differences in hormone levels between determinations at 0, 20 and 60 min, 0 vs 20 min and 0 vs 60 min, 20 vs 60 min, the differences did not appear to have clinical significance.

Methods

To evaluate differences between single sample and pool (0’, 20’ and 60’) determinations for assessing prolactin, FSH and LH levels.

Results

We found differences between prolactin levels in determinations at 0’, 20’ and 60’ (21.5±64.6 vs 20.0±63.9 ng/ml, P < 0.001). The mean difference between prolactin levels at 0’ and 20’ was 1.8±7.6 ng/ml at 0’ and 60’ 2.8±8.6 ng/ml and at 20’ and 60’ 1.0±7.1 ng/ml. Regarding FSH pools there were also found differences in hormone levels between determinations at 0’, 20’ and 60’ and between the FSH level at 0’ and the mean of the three determinations (20.9±27.3 vs 20.1±20.4 vs 10.0±26.3 mlU/ml, P < 0.001; 20.9±27.3 vs 20.3±26.6 mlU/ml, P < 0.001), and the same was observed for LH pools (11.9±12.8 vs 11.4±12.3 vs 11.0±12.1 mlU/ml, P < 0.001; 11.9±12.8 vs 11.4±12.3 vs 11.0±12.1 mlU/ml, P < 0.001). The mean difference between the FSH levels at 0’ and 20’ was 0.7±2.3 mlU/ml, at 0’ and 60’ 0.9±2.3 mlU/ml and at 20’ and 60’ 0.1±1.9 mlU/ml when considering LH pools the results were 0.5±2.2, 1.2±2.5, and 0.4±1.8 mlU/ml. Conclusion

Despite the presence of differences in hormone levels between pool determinations these differences, given its range, do not appear to have clinical significance.

DOI: 10.1530/endoabs.32.P888

---

Endocrine Abstracts (2013) Vol 32
and prolactin levels after controlling for age at diagnosis \(r = -0.085, P = 0.454\). There were no differences in body mass index \((28.4 \pm 4.8 \text{ vs } 28.9 \pm 6.1 \text{ kg/m}^2, P = 0.678)\), tumor size \((19.3 \pm 15.4 \text{ vs } 15.2 \pm 7.8 \text{ mm}, P = 0.328)\), SDNIA \((19.8 \pm 25.5 \text{ vs } 19.5 \pm 23.1 \text{ ng/ml}, P = 0.959)\), IGFI levels (expressed as a percentage of the upper limit of normal), FSH or LH. No differences were found regarding clinical manifestations or symptoms. When evaluated independently, women and men, we found a higher prevalence of galactorrhea in women with PRL-producing tumors \((14.3 \text{ vs } 4.1\%, P = 0.001)\). When evaluated only premenopausal women \((n = 19)\) we found no differences between the two groups except for the levels of PRL.

Discussion

Tumors with hypersecretion ST and PRL are associated with earlier diagnosis comparing with tumors producing only ST. The shortest time to diagnosis seems especially related to age at diagnosis and not with PRL levels.

DOI: 10.1530/endoabs.32.P890

P890

Macroprolactinomas: dopamine agonists for how long?
Maria Joana Santos1, Rui Almeida1,2 & Olinda Marques1
1Department of Endocrinology, Hospital de Braga, Braga, Portugal; 2Department of Neurosurgery, Hospital de Braga, Braga, Portugal.

Introduction

Dopamine agonists (DA) effectively normalize prolactin secretion and reduce tumor size in most patients with macroprolactinomas. However, some patients are considered partially/total resistant. Some authors propose that patients treated for 2 years, with normal prolactin secretion with low dose AD and maximal tumour diameter reduction >50%, could suspend treatment, but relapse rate is uncertain. Definition of resistance, ideal duration of treatment and criteria to evaluate reduction of tumor size have to be clarified.

Objectives and methods

Observational, analytical and retrospective study to assess the response of macroprolactinomas to DA in the first 2 years of treatment and define three groups of response based on prolactin levels and maximal tumour diameter reduction: resistant (high PRL, <10%); sensitive (normal PRL >50%) and partially resistant (PR) the remaining, and analyze their outcome.

Results

Fifty-two patients, 51.9% males; mean age at diagnosis 40.3 ±16.3 years; mean follow-up 6.8 ± 4.1 years; 90.4% treated with bromocriptine, median initial dose 5.0 mg/day (P25-3.75 mg; P75-7.5 mg). After 2 years, 48% sensitive; 41.9% PR; 10% resistant. After 1 year, sensitive and PR patients normalized PRL in 85 and 50% and reduced tumour size >50% in 50 and 5.9% respectively. In both groups, PRL normalization didn’t improve significantly in the second year. This period was important for imagiologic response in sensitive \(P = 0.003\), but not in PR \(P = 0.003\). In resistant, there wasn’t significant improvement in either parameter after 2 years or afterwards \((P = 0.331)\). At follow-up, 19% of sensitive had withdrawn treatment, without recurrence. Although PR patients improved prolactin normalization \(86.7\%\) \(P = 0.016\) and tumour reduction \((>50\%-53.5\%\); \(P = 0.008\)) at follow-up, they still had a less favourable outcome.

Conclusion

In our series, biochemical response preceded imagiologic response. Therapeutic results after 2 years were already present at 1 year of treatment and were maintained afterwards. PR had a less favourable outcome at follow-up, making their identification important for earlier change of therapeutic approach.

DOI: 10.1530/endoabs.32.P890

P892

Measurement of hGH in acromegalic patients under pegvisomant treatment

Mariana Purice1, Monica Gheorghiu1,2, Simona Jercalau1 & Corin Badiu1,2
1C.I. Parhon National Institute of Endocrinology, Bucharest, Romania; 2C. Davila University of Medicine and Pharmacy, Bucharest, Romania.

Treatment with hormone analogues can challenge the precise measurement by interference with the routinely used immunoassays systems, related to the presence of autoantibodies in the serum, interference with associated therapy or the presence of altered forms of the hormone, with modified biological activity and/or immunoactivity.

In patients with acromegaly treated with the hGH antagonist Pegvisomant (PEG; Somavert), most of the assays are deeply influenced. The current recommendation for assessing secretion status in this setting is by basal IGFI assays. In our study, we performed hGH measurement during OGTT or in a four-points day curve. Six acromegalic patients, four of them treated with 10-30 mg PEG s.c. daily, and two without PEG were evaluated using the following methods: i) 125I-IRMA HGH MAIA Clone (ADALTIS Italy), a liquid phase reaction immunoassay with magnetic separation of antibody-antigen; ii) antibody complex, not corrected for B2036-PEG cross-reactivity \((n = 33\) samples).

Conclusions

In patients with PEG treatment, the correlation between GH values with the two assays was 0.91 and 0.99. In patients treated with PEG, all values obtained with the first method were under the detection limit \(< 0.5 \text{ ng/ml}\). GH levels obtained with the second method were related with the tumor status of each patient, in four out of seven set of data being in a similar range to GH levels before PEG treatment, in two lower and in one higher \((P < 0.05)\). It seems that the second assay does not interfere with B2036-PEG, possibly due to the fact that in this method serum GH, but not PEG, binds directly to the anti-GH antibody that is coated on the tube.

In conclusion, hGH assays in acromegalic patients treated with Pegvisomant must be carefully checked for being appropriate for this specific clinical setting.

DOI: 10.1530/endoabs.32.P892

P893

Myeloproliferative neoplasms in patients with acromegaly

Tatjana Isailovic1, Bojana Beleslin1, Nebojsa Lalic1,2, Ljiljana Lukic1,2, Bojana Popovic1, Milan Petakovic1, Djuro Macur1,2, Sanja Ognjanovic1, Valentina Elezovic1, Ivana Bozic1, Tamara Bogavac1, Dusan Ilic1,2, Tatjana Pekmezovic3 & Svetozar Damjanovic1,2
1Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Centre of Serbia, Belgrade, Serbia; 2School of Medicine, University of Belgrade, Belgrade, Serbia; 3School of Medicine, Institute of Epidemiology, University of Belgrade, Belgrade, Serbia.

Introduction

Hypogonadism is associated with an impaired metabolic profile, particularly in patients with hypogonadism. This study aimed to: i) investigate the effects of short and long treatment with cabergoline (CAB) on the prevalence of metabolic syndrome (MS) and insulin sensitivity and ii) to evaluate the impact of gonadal function on metabolic changes, in male patients with HPRL.

Patients and methods

Nineteen patients \((41 \pm 13.9\) years) with HPRL entered the study. PRL, total testosterone, BMI, waist circumference, lipid and glucose profile and fasting insulin levels were assessed at diagnosis and after short \((12\) months) and long-term \((60\) months) treatment with CAB. NCEP-ATP III criteria were used.

Results

At baseline, the prevalence of hypogonadism was 73% while prevalence of MS was 52%; MS prevalence was higher in patients with \((74\%\) than in those without \((25\%)\) hypogonadism. A significantly higher waist and BMI was found in hypogonadotic than in normogonadotic patients. CAB induced PRL normalization in 74 and 92% of patients after 12 and 60 months respectively. Hypogonadism was found in 42 and 10% after respectively 12 and 60 months, where MS significantly decreased to 10%. Serum triglycerides, total cholesterol, insulin levels, BMI and HOMA-IR were significantly reduced after 12 and 60 months whereas an increase of HFL was registered after 60-month follow-up. CAB dose and PRL changes correlated with the changes in BMI after long-term treatment. Testosterone levels negatively correlated with waist, insulin levels and HOMA-IR either at baseline and after treatment. Testosterone levels was the best predictor of HOMA-IR.

Conclusions

In conclusion, normal testosterone levels play an important role in the amelioration of MS of patients with HPRL by improving of insulin resistance.

DOI: 10.1530/endoabs.32.P893

Endocrine Abstracts (2013) Vol 32
P894
Familial panhypopituitarism by a mutation in PROP1: four of seven brothers affected
Eva Lao1, Paula Freitas1, Eduarda Coutinho2, Manuel Lemos2 & Davide Carvalho1
1Department of Endocrinology, Diabetes and Metabolism, Faculty of Medicine University of Porto, Centro Hospitalar São João, Oporto, Portugal; 2Research Centre for Health Sciences, University of Beira Interior, Covilhã, Portugal.

Introduction
PROP1 (Prophet of Pit-1) mutations are the most frequent genetic cause of panhypopituitarism, a condition associated with a deficiency or inadequate production of hormones of the anterior pituitary. The PROP1 gene encodes a transcription factor involved in the ontogeny, differentiation and function of somatotrophs, lactotrophs and thyrotrophs. These mutations are characterized by a remarkable clinical variability, including time of onset of hormonal deficiencies, hypophysal dimensions and secretion of cortisol.

Case report
We describe a family of consanguineous parents (second-degree cousins), composed of eight siblings, four with panhypopituitarism, followed in department of Endocrinology, three healthy, and one stillbirth. Two brothers, 41 and 43 years of age, had an initial diagnosis of dwarfism at 9 and 12 years old respectively. Subsequently, it was detected TSH, FSH/LH and prolactin deficiency, in both. In the latter it was also diagnosed cortisol deficiency. The two sisters, aged 46 and 50 years old, had the diagnosis of panhypopituitarism with deficiency of GH, TSH, FSH/LH, prolactin and cortisol, since 15 and 9 years old respectively. There was no previous family history of panhypopituitarism. The genetic study was performed in the four brothers, detecting a homozygous mutation in the PROP1 gene (c.301-302delAG).

Conclusion
The three groups did not differ in age, BMI, urinary and midnight cortisol levels at presentation. A significant decline in the incidence of hypertension was noted in group A (from 44.4 to 11.1%, \( P=0.004 \)) and in group B (from 81.8 to 18.2%, \( P=0.01 \)). In group C a similar decline was noted only in group C1 (from 63.2 to 21.1%, \( P=0.03 \)) but not in group C2. In all groups no statistical differences in the incidence of diabetes, osteoporosis/osteopenia and dyslipidemia were observed.

DOIs: 10.1530/endoabs.32.P894

P895
Cushing’s disease in children – the effectiveness and complications of transphenoidal surgery
Przemyslaw Witiek* & Grzegorz Zielinski2
1Department of Endocrinology and Isotope Therapy Military Institute of Medicine, Warsaw, Poland; 2Department of Neurosurgery Military Institute of Medicine, Warsaw, Poland.

Introduction
ACTH-secreting pituitary adenomas are the most common cause of endogenous hypercortisolism in children after 10 years of age. In spite of this pediatric Cushing’s disease (pCD) is a rare medical condition. Transphenoidal surgery (TSS) remains the treatment of choice but – according to literature rate – results of such a procedure could be worse comparatively to adult population. The aim of the study was to evaluate the clinical course, safety, efficacy and complications of TSS for pCD.

Method
Among 312 patients with Cushing’s disease operated on between 2000 and 2011 we identified 11 patients with pCD – five boys and six girls. The mean age was 16.9 years (range: 13–18). The diagnosis was based on commonly adopted hormonal criteria as well as preoperative magnetic resonance imaging. TSS was performed according to the same microsurgical protocol. The remission was assessed based on the early postoperative, subnormal serum cortisol levels (≤2.5) and its dynamics during at least 12 months follow-up.

Results
Growth retardation and overweight or obesity were present in all 11 patients. Hypertension and mental disorders were diagnosed in five of them (45.5%). In all cases, a pituitary microadenoma was precisely visualized in MRI. Based on adopted hormonal criteria nine children (81.8%) were considered to be surgically cured whereas in two patients (18.2%) the persistent CD was confirmed. There were no medical and fatal complications. Transient diabetes insipidus appeared in three patients (27.3%) and syndrome of inappropriate antidiuresis (SIAD) in additional two cases (18.2%). Pituitary insufficiency was observed in one patient (9.1%). There was no case of postoperative cerebral spinal fluid leakage or meningitis.

Conclusions
Clinical manifestation and gender distribution of pCD is different comparatively to adult population. In spite of this TSS is a safe and effective treatment leading to a high rate of biochemical remission, similar to observed in adults.

DOIs: 10.1530/endoabs.32.P895
Acromegaly is a disease characterized by the excessive growth of bones and soft tissues due to prolonged secretion of growth hormone (GH) by the pituitary gland. The condition affects both men and women and is often associated with other health problems, including an increased risk of certain cancers. The prevalence of acromegaly is relatively low, but the disease has a significant impact on the quality of life for affected individuals.

In patients with active acromegaly, serum GH but not IGF1 levels correlate with body composition parameters compared to eugonadal male acromegalics. Serum GH in men (30.3 ± 9.4 mIU/L) correlated significantly negatively with Fat% (r = -0.65, P < 0.05). Serum IGF1 did not correlate significantly with any of the body composition parameters compared to eugonadal female acromegalics (n = 24 females and 16 males, 48.9 ± 6.4 years old, with BMI of 28.04 ± 1.27 kg/m², diagnosed 4.15 ± 1.09 years ago), body composition was analyzed by dual-energy X-ray absorptiometry (DEXA) Hologic- W-QDR. Total body fat mass (FM), total body lean mass (LM), total body fat percent (Fat%), abdominal fat mass (abFM), abdominal lean mass (abLM) and abdominal fat percent (abdFat%) were correlated to serum GH and IGF1 values. Gonadal status and replacement therapy were assessed in all patients.

In patients with active acromegaly, serum GH but not IGF1 levels correlate with body composition parameters compared to eugonadal male acromegalics. Serum GH in men (30.3 ± 9.4 mIU/L) correlated significantly negatively with Fat% (r = -0.65, P < 0.05). Serum IGF1 did not correlate significantly with any of the body composition parameters compared to eugonadal female acromegalics (n = 24 females and 16 males, 48.9 ± 6.4 years old, with BMI of 28.04 ± 1.27 kg/m², diagnosed 4.15 ± 1.09 years ago), body composition was analyzed by dual-energy X-ray absorptiometry (DEXA) Hologic- W-QDR. Total body fat mass (FM), total body lean mass (LM), total body fat percent (Fat%), abdominal fat mass (abFM), abdominal lean mass (abLM) and abdominal fat percent (abdFat%) were correlated to serum GH and IGF1 values. Gonadal status and replacement therapy were assessed in all patients.

Results

Serum GH in men (30.3 ± 9.4 mIU/L) correlated significantly negatively with Fat% (r = -0.65, P < 0.05). Serum GH in females (49.2 ± 18.1 mIU/L) correlated significantly positively with LM (48.03 ± 7.3 kg, r = 0.48, P < 0.05). Serum IGF1 did not correlate significantly with any of the body composition parameters compared to eugonadal male acromegalics (n = 4) but did not differ in any of the body composition parameters compared to eugonadal male acromegalics (n = 9) or hypogonadal patients on testosterone (n = 3). Hypogonadal and menopausal women (n = 19) exhibited significantly elevated FM (23.1 ± 2.2 vs 19.3 ± 2.1 kg; P < 0.05), abFM (28.3 ± 0.4 vs 23.0 ± 0.3 kg; P < 0.05) compared to the smaller number of eugonadal female acromegalics (n = 5).

Conclusion

Important body composition parameters (lean body mass, total body fat percent) correlate with GH levels but not with IGF1 in both men and women with active acromegaly. Ratine serum GH level assessment should be added to serum IGF1 determination in the assessment of the acromegaly activity. Gonadal status appears to affect the body composition in female than in male active acromegaly.

DOI: 10.1530/endoabs.32.P987

Receptor expression in craniopharyngiomas causing tumor growth in pregnancy: case report and review of the literature

Tome Monica, Vroonen Laurent, Thiry Albert, Daly Adrian & Beckers Albert
Centre Hospitalier Universitaire de Liège, Liège, Belgium.

Introduction

Craniopharyngiomas (CP) are benign tumors that arise from remnants of the Rathke’s pouch. Clinically, they are classified as cystic or calcified tumors. The presence of hormonal receptors in CP has been reported in in vitro studies but only eight cases growing during pregnancy have been published in literature.

Case report

We report a 3-year-old woman who was initially diagnosed with a prolactin secreting tumor with rapid enlargement during pregnancy that eventually was found to be an aggressive CP. Pregnancy was achieved with IVF. The patient had a medical history of hyperprolactinemia treated with cabergoline and a pituitary tumor of 9 mm. She consulted at 27 weeks of gestation because of visual impairment. A pituitary MRI showed a cystic pituitary tumor of 22 mm in maximum diameter with suprasellar extension and compression of the optic apparatus. A second 8 mm tumor was described in the floor of the fourth ventricle. Visual assessment had demonstrated no deficit before pregnancy. By the 33rd week of gestation the subject had right lateral homonymous hemianopia with a decreasing visual acuity that resulted in blindness of the left eye and diabetes insipidus; a caesarean section was performed at that time. The newborn was healthy. Neurosurgery was performed postpartum by a sub-frontal approach. The pathology confirmed an adamantinoma.

Conclusion

IVF allows pregnancy in infertile population. Only eight cases of CP growing during pregnancy have been reported. We have demonstrated expression of hormonal receptors that may explain the aggressive behaviour of CP during pregnancy. This is the only report with an associated ependymoma.

DOI: 10.1530/endoabs.32.P989

Severe hyponatraemia due to SIADH is associated with very high 5-year mortality

Ansu Basu1,2 & Robert Ryder1,2
1City Hospital, Birmingham, UK; 2University of Birmingham, Birmingham, UK.

Purpose/background

SIADH is a common cause of severe hyponatraemia in hospital and is due to a variety of underlying aetiologies. Kidney injury (KI) which may be associated with severe hyponatraemia is associated with poor clinical outcomes. It is unclear whether severe hyponatraemia due to SIADH is also linked to adverse outcomes. We therefore compared the 5-year outcome (mortality) in patients with severe hyponatraemia (Na ≤ 125 mmol/l) caused by SIADH with those due to kidney injury.

Methods

Retrospective observational cohort analyses of anonymised data over a 3-year period. All patients had a mean Na ≤ 125 mmol/l. Additional criteria used were – KI: urea > 7.5 mmol/l, creatinine > 130 µmol/l and SIADH: urea < 3.6 mmol/l, creatinine < 130 µmol/l. Mortality data was reviewed up to 5 years from the date of the last test and was right-censored at 5 years.

Results

Mean (s.d.) serum sodium levels were 121.5 (± 4.0) and 122.1 (± 3.0) mmol/l in those with SIADH (n = 326) and KI (n = 313) respectively. The corresponding values of serum urea were 2.6 (0.7) and 22.0 (11.1) mmol/l. 73.4% of patients with KI died within the first year after admission; the corresponding figure for SIADH patients was 56.0%. At 5-year the corresponding mortality figures were 86.7% (KI) and 79.0% (SIADH). Kaplan-Meir curves showed a statistically significant (log-rank, P < 0.0001) shorter median survival time for patients with KI (1.19 months (95% CI 0.70, 1.67)) compared to those with SIADH (22.8 months (95% CI 14.84, 30.73)). This difference in survival was maintained with data standardised for age at death.

Conclusions

SIADH is associated with a high first year mortality after discharge albeit less than those with KI. At 5-years the mortality rates appear to converge. This interesting observation may suggest a role of V-2 receptor antagonists in improving medium-to-long-term outcomes in some patients with SIADH.

DOI: 10.1530/endoabs.32.P999

Increased thyroid cancer risk in acromegaly

Selcuk Dagdelen, Nese Cinar & Tomris Erbas
Department of Endocrinology and Metabolism, School of Medicine, Hacettepe University, Ankara, Turkey.

Introduction

Acromegaly increases cancer risk. We aimed to determine the prevalence and the predictors of tumors in acromegalic patients treated at our department.

Design

We retrospectively evaluated 142 acromegalic patients (75 females (mean age 52.1 ± 10.4 years and 67 males (mean age 49.4 ± 12.7 years)) treated at university center, endocrinology outpatient clinic between 1990 and 2012, with a mean follow-up duration of 7.5 ± 5.9 years. The patients were screened with colonoscopy, mammography, thyroid and prostate ultrasonography.

Results

Malignancy was found in 31 (21.8%) patients. No significant difference was observed in the distribution of malignancy among sexes (20.0% in females vs 23.9% in males). Thyroid cancer was the most frequent (n = 15, 10.6%) followed by the breast cancer (n = 4, 2.8%) and colorectal cancer (n = 4, 2.8%). Renal cell cancer in 2 patients, oddi tumour in one, rectal carcinoid tumor in one, bladder cancer in one, malignant melanoma in one, prostate cancer in one, lung cancer in one, parotid mucoepidermoid carcinoma in one and malign mesenchymal tumor in brain in one patient were detected. One patient had both thyroid and renal cell cancer. The patients with cancer were significantly older than the patients without cancer and age of patients at diagnosis of acromegaly was significantly higher in patients with cancer (45.8 ± 9.9 vs 40.7 ± 11.6 years, P < 0.05). No significant difference was found in duration of the disease, initial GH levels, the prevalence of diabetes, hypertension, coronary heart disease, hyperlipidemia and treatment modalities between the patients with/without cancer.

Conclusion

The risk of cancer in acromegaly especially the thyroid cancer risk seems to be more increased than known in the literature. Therefore, acromegalic patients should be screened routinely for cancer, especially for thyroid cancer due to its being up to three times higher prevalence than breast and colorectal cancer.

DOI: 10.1530/endoabs.32.P900
Efficacy and safety of lanreotide in combination with pegvisomant in clinical practice in patients with active acromegaly with monotherapy failure

Eva Venegas1, Tomás Lucas2, Mónica Marazuela1, Guillem Quatreucar3, Maria Angeles Galvez1, Enrique Romero4, Francisco Morales4, Susan M Webb8, Betina Biaggeti9, Juan José Diaz10, José Antonio Mato11, Ricardo Vilchez1, Ignacio Bernabeu1, Miguel Paja1, Antonio Pico2, Manuel Puig Domingo1, Alfredo Soto1 & on behalf of ACROCOMB study group17

1Hospital Universitario Virgen del Rocío, Sevilla, Spain; 2Hospital Universitario Puerta de Hierro, Majadahonda, Spain; 3Hospital Universitario La Princesa, Madrid, Spain; 4Hospital Universitario Reina Sofía, Córdoba, Spain; 5Hospital Clínico Universitario, Valladolid; 6Hospital Universitario Infantana Cristina, Badajoz, Spain; 7Hospital e IIB Sant Pau, CIBERER 747, Barcelona, Spain; 8Hospital Universitario. Vall d’Hebron, Barcelona, Spain; 9Hospital Universitario Ramón y Cajal, Madrid, Spain; 10Hospital Universitario Virgen de las Nieves, Granada, Spain; 11Hospital Clínico Universitario, Santiago de Compostela, Spain; 12Hospital Clínico Universitario, Bilbao, Spain; 13Hospital General Universitario de Alicante, Alicante, Spain; 14Hospital Universitario Carlos Haya, Málaga, Spain; 15Hospital Universitario Puerta de Hierro, Majadahonda, Spain; 16Hospital Universitario Carlos Haya, Málaga, Spain; 17Hospital Universitario de Pontevedra, Pontevedra, Spain; 18Hospital Severo-Ochoa, Leganés, Spain; 19Hospital Universitario La Princesa, Madrid, Spain; 20Hospital Universitario Virgen del Rocío, Sevilla, Spain; 21Hospital Universitario Germans Trias i Pujol, Badalona, Spain; 22ACROCOMB study, Spain, Spain.

Introduction

ACROCOMB is a retrospective Spanish Multicenter study, designed to evaluate the efficacy (extent of tumour control) and safety of lanreotide (LAN) treatment combined with pegvisomant (PEG) or cabergoline in acromegalic patients with monotherapy failure.

Methods

Patients with acromegaly treated with LAN+PEG (45% of ACROCOMB patients) at 44 Spanish Endocrinology Departments were analysed.

Results

40% of patients were male, median age: 42.5 years. Mean time from diagnosis was 7.2±7.5 years. Tumour size at diagnosis was 25.5±9.9 mm. 92% of patients had surgery and 65% had radiotherapy. Immediately prior to LAN-PEG, 57% were receiving LAN, 4% octreotide, 35% PEG, 2% cabergoline and one patient was not receiving treatment. Median baseline IGF1 was 156% ULN (15–534%), LAN+PEG was indicated for monotherapy failure (85%), tumoural volume control (12%), headache (8%), 14% of patients received LAN+PEG for >1 reason. Median LAN+PEG treatment duration was 2.1 years (0.4–6.3). Median monthly LAN doses were similar at baseline (120 mg (60–240)) and at end of study (EOS) (120 mg (30–240)). At baseline 21% of patients were receiving an extended LAN regimen (q12w or q4w) and at EOS 25%. Median weekly PEG doses increased from 70 mg (10–210) at baseline to 105 mg (30–210) at EOS; Median IGF1 values decreased by 6 months (83% ULN (11–236%), P < 0.0001) and remained stable at EOS (84% ULN (25–345%), P < 0.0001). At EOS 71% of patients had normal IGF1 values; drug infusions might explain lack of normalization in the other patients. Tumour size decreased in 3 patients. No changes in hepatic, cardiac, glycemic parameters were reported. 41 (79%) patients continue receiving LAN+PEG at EOS.

Conclusion

The combination of LAN and PEG is well-tolerated and has high efficacy in clinical practice in patients not well controlled with monotherapy. No significant liver enzyme elevations were observed.

DOI: 10.1530/endoabs.32.P901

Efficacy of hGH treatment in pituitary dwarfish- age does matter

Jeanina Idriceanu, Ioana Vasiliu, Ramona Popovici, Ioana Bodescu, Cristina Rusu, Voichita Mogos & Carmen Vulpoi

University of Medicine and Pharmacy 'Gr.T.Popa', Iasi, Romania.

Introduction

The spectrum of GH deficiency (GHD) in children ranges from complete deficiency, with severe growth retardation, to partial deficiency, with slightly short stature. The administration of GH to children with GHD improves linear growth, mainly during the first 2 years of treatment.

Patients and methods

The study analyzes pattern of growth in 35 children (24 boys, 11 girls) with GHD, in the first year of treatment with hGH. There were three groups, according to pubertal stage ( Tanner): < 8 years (prepubertal) – one girls (G) and one boy (B), 8–12 years (PIII B, PIIB II G, PIIG II B) – 2G, 2B and ≥ 12 years (minimum PIIIIB III G, PIIGII B) – 3G, 3B.

Results

Before treatment, SDS for height was – 2.5. All had GHD biological confirmed and delayed bone age. The analysis showed: 1B-average growth rate 0.89 cm/month in the first 6 months, similar in the next 6 (0.83 cm/month), mean height gain 9.72 cm ± 2.6 and bone age (BA) improved with 13.1 months; 1G-average rate higher in the first month (1.02 cm/month), compared to the next 6 (0.67 cm/month), mean gain 10.2 cm±2.3 BA improved with 18.5 months; 2B-average rate 0.63 cm/month in the first 6 months, similar in the next 6 (0.61 cm/month), mean gain 7.3 cm±0.77 BA improved with 17.5 months; 2G-average rate 0.63 cm/month in the first 6 months, 0.78 cm/month in the next 6, mean gain 8.55 cm±1.63 BA improved with 9 months; 3B-average rate 0.72 cm/month in the first 6 months, 0.63 cm/month in the next 6, mean gain 7.94 cm±0.83 BA improved with 15.4 months; 3G-one patient with growth rate 0.6 cm/month in the first 6 months, similar in the next 6, height gain 7.3 cm BA improved with 24 months.

DOI: 10.1530/endoabs.32.P902
Discussions
We noticed a negative correlation between growth rate and age of beginning treatment. Despite hGH dose adjustment, the growth rate remains lower in children diagnosed later, confirming the importance of an early diagnosis and treatment, prepubertal.

DOI: 10.1530/endoabs.32.P9003

P904
Clinical, hormonal and radiological characteristics of a group of primary empty sella patients
Arzu Gedik1, Merve Yilmaz1, Teyfik Demir1, Firat Bayraktar1, Suleyman Men1, Sevins Eraslan1 & Abdurrahman Comlekci1,2
1Endocrinology Department, Medical Faculty, Dokuz Eylul University, Izmir, Turkey; 2Biochemistry Department, Medical Faculty, Dokuz Eylul University, Izmir, Turkey.

Background
Primary empty sella is an anatomical term defining the herniation of subarachnoid space within the sella turcica without an underlying factor such as pituitary tumor, surgery, irradiation or trauma.

Methods
We retrospectively evaluated clinical, hormonal and radiological data of the patients with primary empty sella syndrome followed in our institution between 2001 and 2012.

Results
Ninety-four patients (80 (85.1%) females) were included in the study. The mean age of the patients at diagnosis was 50.3±15 years (15–85). Fatigue and headache were the most common presenting symptoms (47.9 and 42.6% respectively). Menstrual irregularity in women (25%) and impotence in men (35%) were the most common sex specific symptoms. In addition galactorrhea, visual abnormalities, loss of libido were also recorded at a lesser extent. Of the risk factors of primary empty sella, multiparity was detected in 80% of the female patients and hypertension in 29.8%, weight excess in 44.7%, autoimmune thyroid disorder in 12.8% of the whole study group. Patients were evaluated for pituitary function with basal hormone levels and dynamic testing when necessary. At least one pituitary hormone deficiency was found in 67% of cases. Growth hormone deficiency was the most common (54.3%) hormonal abnormality. Secondary adrenal insufficiency (43.6%), hypogonadotropic hypogonadism (33%), central hypothyroidism (25.5%), mild hyperprolactinemia (24.5%), and diabetes insipidus (5.3%) were also recorded. Thirty-two percent of the patients had partial and the remaining 68% total empty sella in pituitary imaging. No significant differences were found among the partial and total empty sella subgroups in terms of hormonal deficiency.

Conclusion
Primary empty sella appears to be more frequent in multiparous women and in individuals with obesity. Radiological discrimination as partial or total empty sella seems to have no effect on the degree of hypopituitarism.

DOI: 10.1530/endoabs.32.P9004

P905
The effects of cabergoline treatment on cardiac valves in patients with prolactinoma
Fulin Saracı1, Sefa Saracı2 & Pelin Tutuncuoglu2
1Department of Internal Medicine, Medical Faculty, Ege University, Izmir, Turkey; 2Department of Cardiology, Ataturk Training and Research Hospital, Izmir, Turkey.

Introduction
Dopamine agonists have been reported to increase the risk of cardiac valve regurgitation in valve disease risks for 3 years treatment with cabergoline in patients with prolactinoma. The aim of the study was to evaluate the frequency of cardiac valve diseases and regurgitation in patients with prolactinoma at the end of 3 years.

Methods
Thirty-one patients with prolactinoma who had received cabergoline following 3 years were enrolled study. Two-dimensional and Doppler echocardiography were performed before treatment and after 3 years. All records were evaluated in all patients, retrospectively.

Results
Before treatment, 2 (2/31) patients had minimal mitral valve regurgitation and 1 (1/31) patient had minimal tricuspid insufficiency. Thickening of the mitral, tricuspid and aortic valves were not found before treatment. After 3 years, 1 (1/31) patients had moderate mitral valve regurgitation and 1 (1/31) patient had moderate tricuspid valve regurgitation. There were no statistically significantly differences of diameters of valves areas between two measurements (Table 1).

Conclusion
Cabergoline therapy for 3 years was not associated with an increased risks of cardiac valve diseases and regurgitation in patients with prolactinoma.

DOI: 10.1530/endoabs.32.P9005

P906
Treatment with pasireotide LAR normalizes prolactin levels in patients with acromegaly and hyperprolactinemia: randomized, double-blind, 12-month, phase III study
Annamaria Colao1, Pamela Freda2, Feng Gu3, Karina Hermosillo Resendiz4, Matthieu Ruffin5, YinMiao Chen6 & Marcello Bronstein7
1Università Federico II di Napoli, Naples, Italy; 2Columbia University College of Physicians and Surgeons, New York, New York, USA; 3Peking Union Medical College Hospital, Beijing, China; 4Novartis Pharmaceuticals Corporation, Florham Park, New Jersey, USA; 5Novartis Pharma AG, Basel, Switzerland; 6University of Sao Paulo Medical School, Sao Paulo, Brazil.

Introduction
Around 20–30% of patients with acromegaly have hyperprolactinemia, which is associated with infertility and gonadal sexual dysfunction. Current therapy involves somatostatin analogues for GH/IGF1 excess and a dopamine agonist to decrease prolactin levels. The objectives of this analysis were to assess treatment with pasireotide LAR or octreotide LAR alone in patients with acromegaly and hyperprolactinemia.

Methods
Patients with acromegaly (GH ≥ 5 µg/l or GH nadir ≥ 1 µg/l post-OCTT, and IGF1>ULN) who were de novo with a visible adenoma on MRI or medically naive (no previous medical therapy but prior pituitary surgery) received pasireotide LAR 40 mg/28 days (n = 176) or octreotide LAR 20 mg/28 days (n = 182) for 12 months; dose titration (to pasireotide LAR 200/60 mg or octreotide LAR 10/30 mg) was permitted. This analysis focuses on the efficacy/safety of pasireotide LAR and octreotide LAR in patients with baseline hyperprolactinemia (prolactin above age/sex-matched ULN).

Results
29 (16.5%) pasireotide LAR and 30 (16.5%) octreotide LAR patients had baseline hyperprolactinemia (mean prolactin 83.5 and 55.9 µg/l, respectively). After 12 months, 21/29 (72.4%; 95% CI 52.8, 87.3) pasireotide LAR and 17/30 (56.7%; 95% CI 37.4, 74.5) octreotide LAR patients had normalized prolactin levels; 8/30 (26.7%) had normal IGF1, respectively. After 12 months, mean prolactin decreased by 60.4 and 39.6%, mean GH decreased by 71.1 and 67.6%, and mean IGF1 decreased by 41.1 and 39.6%, respectively, in pasireotide LAR and octreotide LAR patients. Tumor volume decreased by ~40% in both treatment groups. Pasireotide was well tolerated and most adverse events were mild/moderate; hyperglycemia-related adverse events were more common with pasireotide LAR than octreotide LAR.

Conclusions
In this subset of patients with baseline hyperprolactinemia, pasireotide LAR normalized prolactin in >70%, normalized IGF1 in ~25% and achieved GH <2.5 µg/l in ~35% of patients. Pasireotide may be an effective treatment for patients with a GH- and prolactin-secreting pituitary adenoma.

DOI: 10.1530/endoabs.32.P9006

P907
Characteristics and outcomes of the Italian subpopulation enrolled in the observational, multicenter hypopituitary control and complications study (HypoCCS)
Gianluca Aimaretti1, Diego Ferone2, Maria Rosaria Ambrosio1, Paolo Beck-Peccoz2, Salvatore Cannavò3, Anna Maria Colao1, Marco Lossa1, Beverly Festin Martinez4, Paolo Marchi1 & Alessandra Vottero5
1Department of Translational Medicine, University of the Eastern Piedmont, Novara, Italy; 2Endocrinology Unit, Department of Internal Medicine and
Sleep-apnea and cardiomyopathy in acromegalic patients

Ruth Sanchez-Ortiga, Alfredo Candela, Vicente Climent, Laura Sanchez-Tejada, Irene Monjas-Canovas, Javier Abarca, Oscar Moreno-Perez & Antonio Pico
Hospital General Universitario Alicantino, Alicante, Spain.

Introduction
Sleep disordered breathing (SDB) promotes structural myocardial changes and can trigger cardiac arrhythmias. Acromegalic patients have high prevalence of SDB and GH-IGF1 excess is related to a specific cardiomyopathy characterized by concentric cardiac hypertrophy and diastolic dysfunction. The aim of this study was to assess the relationship between SDB and cardiac dysfunction on acromegalic patients.

Material and methods
Observational descriptive study of 32 acromegalic patients (14 men, 50.3 ± 11.4 years, 21 treated with somatostatin analogues (SSA) and 20 patients referred to the respiratory department for SDB study paired with acromegalic patients in sex, age and BMI (10 men, 53.2 ± 12.7 years). Polysomnography, echocardiography and electrocardiography (ECG) were performed in all patients. Patients were defined having sleep-apnea (SA) if they had more than ten apneas or hypopneas per hour. Pearson, t-Student and χ² tests were used for statistical analysis.

Results
24 (75%) acromegalic patients and 15 (78.9%) controls had SA, all of them due to obstructive cause. 18 (58.1%) acromegalic patients and 6 (30%) controls had diastolic dysfunction of left ventricle (P=0.05). Patients with/without SSA did not have different prevalence of SA or cardiac dysfunction. Only acromegalic patients, but not controls, with SA compared with those without SA had higher diastolic LV diameter (49.7 ± 6.9 vs 44.7 ± 5.7, P=0.02) and higher pulmonary artery systolic pressure (35.3 ± 4.5 vs 22.0 ± 7.6, P=0.01). Moreover, they had a trend toward lower mean heart rate (72.6 ± 7.7 vs 78.1 ± 9.1, P=0.08), less ejection fraction (62.6 ± 12.7 vs 71.4 ± 10.4, P=0.09) and more alterations on ECG (50 vs 12.5%, P=0.09).

Conclusions
Sleep apnea is a risk factor to cardiac abnormalities in acromegalic and non acromegalic people. The prevalence of cardiac abnormalities in acromegaly is higher when SA is present, independent of the cure or control of acromegaly.

DOI: 10.1530/endoabs.32.P909


Ionela Băcuă1, Simona Galoiu2, Cristina Capatină1,2, Ileana Botus1,3, Anda Dumitrascu2, Vasile Ciubotaru2, Mihail Cuculescu1,2, Catalina Poiașă1 & Serban Raduă1
1Carol Davila University of Medicine, Bucharest, Romania; 2Constantin I. Parhon National Institute of Endocrinology, Bucharest, Romania; 3Department of Molecular Medicine and Surgery, Karolinska Institutet, Rolf Luft Research Center for Diabetes and Endocrinology, Stockholm, Sweden; 4Department of Neurosurgery, Bagdasar-Arseni Emergency Hospital, Bucharest, Romania; 5William Harvey Research Institute, Queen Mary University of London, London, UK.

Introduction
We have recently described a novel AIP mutation c.940C>T; p.R314W, in a young sporadic acromegaly patient.

Aim

Patients and methods
One sporadic acromegaly patient, investigated by sequencing screening of all six AIP exons, following informed consent, as part of a sporadic pituitary adenoma cohort. 110 control subjects without clinical signs of pituitary adenoma (24M/86F) were screened for AIP exon 6 sequence changes using high resolution melting analysis of exon 6 PCR products.

Conclusions

DOI: 10.1530/endoabs.32.P910
Results
Sequencing of AIP revealed two heterozygous missense mutations in the acromegaly patient (female, 51 years old at diagnosis). The previously described c.904C>T, p.R314W was present together with a novel sequence change, c.878A>T, p.E293V. The patient presented a large somatotropinoma (30 mm) with perisellar invasion, optic chiasm syndrome, secondary diabetes mellitus, hypertension, and pituitary gonadotroph deficiency. Following initial transphenoidal surgery a tumor remnant was present and required a second transphenoidal intervention and pituitary radiotherapy for controlling tumor growth. Somatostatin analogues therapy could not achieve optimal control of GH secretion. p.R314W and p.E293V were absent 110 controls. In silico evaluation of pathogenicity (Polyphen2) of p.R314W suggested this is pathogenic, while p.E293V scored as non-pathogenic, AIP mutation screening of family members of the index case has not yet been performed.

Conclusion
We describe a novel case of AIP p.R314W mutation. This likely pathogenic mutation has been exclusively associated with sporadic acromegaly to date. Although the reported cases are apparently unrelated, we cannot exclude a founder effect in the Romanian population. In vitro experiments are necessary for confirming the pathogenic role of this novel AIP mutation and understanding the mechanism of its deleterious effect.

Acknowledgments
This work was supported by CNCSIS TE 227/2010 grant from the Romanian Ministry of Education.

DOI: 10.1530/endoabs.32.P910

P911
The p.R16H AIP sequence variant is relatively frequent in Romanian sporadic pituitary adenoma patients
Serban Radian1,2, Jonela Baciu1, Cristina Capatina1,3, Ileana Botusan1,4, Vasilie Ciubotaru1, Anda Dumitrescu1, Mihail Coculescu1,3 & Catalina Poinar1,3
1Carol Davila University of Medicine, Bucharest, Romania; 2William Harvey Research Institute, Queen Mary University of London, London, UK; 3Constantin I. Parhon National Institute of Endocrinology, Bucharest, Romania; 4Department of Molecular Medicine and Surgery, Karolinska Institutet, Rolf Luft Research Center for Diabetes and Endocrinology, Stockholm, Sweden; 5Department of Neurosurgery, Bagdasar-Arseni Emergency Hospital, Bucharest, Romania.

Background
A large spectrum of AIP gene mutations has been identified in familial and sporadic pituitary adenomas (PA) with over 70 different mutations described to date. c.47G>A, p.R16H is an AIP exon 1 variant of unknown significance, its contribution to pituitary adenoma development being controversial.

Aim
Characterization of p.R16H prevalence in a large Romanian cohort of PA patients and controls.

Patients and methods
sporadic PA patients (95F/60M), mean age at symptoms onset 32 years old, were screened by sequencing of all six AIP exons and 108 control subjects (23M/85F) were screened by high resolution melting analysis of AIP exon 1 PCR products.

Results
We identified a heterozygous c.47G>A, p.R16H sequence change in four PA patients (2.58%) (1M/3F): one female acromegaly patient (35 years old at onset) with a macro-somatotropinoma resistant to somatostatin analogues, two female macroprolactinoma patients (23 and 26 years at onset) and one male nonfunctioning agressive PA (NFPA) (38 years at onset), confirmed by sequencing to be heterozygous p.R16H. She had intellectual disability.

Conclusion
We retrospectively analyzed medical records of 151 patients with acromegaly (83 females) followed in our department from 2001 to 2012.

Results
Overall, cancer was detected in 19 (12.6%) patients. Thyroid carcinoma was the most common cancer (n = 9 (5.9%)) and papillary thyroid cancer was the leading type (n = 7 (4.6%)). Besides, one patient had medullary and another one had synchronous papillary and medullary thyroid cancer. Lung cancer was found in two patients and rignet-ring-cell colon carcinoma in one, endometrium cancer in one, malignant melanoma in one and myelodysplastic syndrome in one patient. In addition, four patients had multiple endocrine neoplasia-type 1. Frequency of cancer among both sexes were not significantly different (female: 12/83 (14.4%), male: 7/68 (10.2%), P > 0.05). Cancer was detected in 13 patients after, in four patients simultaneously and in three patients before the diagnosis of acromegaly. There were no significant differences in age of onset of acromegaly or cancer, disease duration, hormone levels and metabolic parameters among the patients with and without cancer. In logistic regression model, neither disease duration nor hormonal activity were associated with malignancy risk.

Conclusion
In parallel with most of the reports, thyroid cancer was the most common cancer in our acromegaly patient group. Although we could not demonstrate an association of disease activity with cancer, high hormone levels with possible mitogenic activity might be a causative or accelerating factor in carcinogenesis.

Acknowledgments
This work was supported by CNCSIS TE 227/2010 grant from the Romanian Ministry of Education.

DOI: 10.1530/endoabs.32.P911

P912
Prevalence of cancer in acromegaly patients; a single center data
Arzu Gedik, Merve Yilmaz, Tevfik Demir, Serkan Yener, Firat Bayraktar, Sevînc Eraslan & Abdurrahman Comlekci
Endocrinology Department, Medical Faculty, Dokuz Eylul University, Izmir, Turkey.

Introduction
The growth promoting effects of GH and IGF1 has lead to increasing number of cancer surveillance studies in acromegaly so far. We herein aimed to present the prevalence of cancer in acromegaly patients followed in our institution.

Patients and design
We retrospectively analyzed medical records of 151 patients with acromegaly (83 females) followed in our department from 2001 to 2012.

Results
Overall, cancer was detected in 19 (12.6%) patients. Thyroid carcinoma was the most common cancer (n = 9 (5.9%)) and papillary thyroid cancer was the leading type (n = 7 (4.6%)). Besides, one patient had medullary and another one had synchronous papillary and medullary thyroid cancer. Lung cancer was found in two patients and rignet-ring-cell colon carcinoma in one, endometrium cancer in one, malignant melanoma in one and myelodysplastic syndrome in one patient. In addition, four patients had multiple endocrine neoplasia-type 1. Frequency of cancer among both sexes were not significantly different (female: 12/83 (14.4%), male: 7/68 (10.2%), P > 0.05). Cancer was detected in 13 patients after, in four patients simultaneously and in three patients before the diagnosis of acromegaly. There were no significant differences in age of onset of acromegaly or cancer, disease duration, hormone levels and metabolic parameters among the patients with and without cancer. In logistic regression model, neither disease duration nor hormonal activity were associated with malignancy risk.

Conclusion
In parallel with most of the reports, thyroid cancer was the most common cancer in our acromegaly patient group. Although we could not demonstrate an association of disease activity with cancer, high hormone levels with possible mitogenic activity might be a causative or accelerating factor in carcinogenesis.

Acknowledgments
This work was supported by CNCSIS TE 227/2010 grant from the Romanian Ministry of Education.

DOI: 10.1530/endoabs.32.P912

P913
Comparison of insulin tolerance test and ACTH stimulation test for evaluation of hypocortisolism in patients with acromegaly
Sine Lyngvi Fougner1 & Sven M Carlsen1,2
1Department of Endocrinology, St Olavs Hospital, Trondheim University Hospital, Trondheim, Norway; 2Unit for Applied Clinical Research, Institute for Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway.

Background
The insulin tolerance test (ITT) is considered the gold standard test for evaluating the ACTH-cortisol axis in patients with pituitary disease. However, the test requires time and personnel resources, and has clear contraindications. Therefore, an ACTH stimulation test is often performed instead.

Objective
The objective was to compare the cortisol response acquired by ACTH stimulation and during ITT in patients with pituitary disease.

Methods
In a total of eight patients with acromegaly, both ITT and an ACTH stimulation test were performed during the same week, but on separate days. A total of 20 comparisons were performed, five being preoperative and 15 postoperative.

Results
Five comparisons were excluded for analyses due to inadequate hypoglycaemia. The remaining 15 comparisons were both preoperative (three, including one after octreotide treatment) and postoperative (three at 3 months, three at 1 year and six at 5 years postoperative). During ITT, peak cortisol level was 637/745 nmol/l (mean/median). Peak cortisol after ACTH stimulation was 948/1040 nmol/l. The discrepant results between cortisol response during ITT compared to stimulation test resulted in peak cortisol 550 nmol/l. The discrepant results between cortisol response during ITT compared to stimulation test resulted in peak cortisol < 550 nmol/l. The discrepant results were pre-treatment, 3 months and 5 years postoperative.

Conclusion
There is some discrepancy between cortisol response during ITT compared to ACTH stimulation test, where the latter leads to a higher peak cortisol level and less often a blunted response when using the same cut-off level.

Acknowledgments
This work was supported by RCN grants 1713 and 1728.

DOI: 10.1530/endoabs.32.P913
Twenty-eight patients with active acromegaly (14 women; age 48.0 ± 9.8 years) were enrolled in the study. The control group comprised 28 age- and sex-matched healthy individuals. Bone turnover markers (osteocalcin, β-crosslaps, and bone alkaline phosphatase) were measured at enrollment and 6 months after achievement of disease remission. Transsphenoidal surgery was performed in all patients. Twenty-one patients achieved disease remission after surgery. In seven patients disease remission was achieved using somatostatin receptor analogs plus radiosurgery in two of them.

Results
Patients with active acromegaly had significantly higher levels of osteocalcin (P<0.003), β-crosslaps (P<0.001) and bone alkaline phosphatase (P<0.001) than the control group. Six months after remission achievement, the patients with acromegaly had significantly lower levels of osteocalcin (P=0.003) and β-crosslaps (P=0.007) than before the treatment. Activity of bone alkaline phosphatase tended to lower, but the difference was not significant between the two measurements. No differences were found in osteocalcin level between the patients in remission and the control group (P=0.09), while the crossovers level as well as the activity of alkaline phosphatase was still significantly higher in the acromegaly remission group (P=0.04 for both parameters).

Conclusion
In patients with acromegaly, 6 months after achievement of disease remission, bone turnover significantly decreases, but still remains higher than in healthy individuals.

DOI: 10.1530/endoabs.32.P915

P916
Skincare in acromegaly
Ramazan Gen1, Elif Sahin Horasan2, Umit Cinkir1, Onur Gultekin2 & Esen Akbay3
1Endocrinology and Metabolism, Mersin University, Mersin, Turkey; 2Infection Disease, Mersin University, Mersin, Turkey.

Introduction
Recent study showed that patients with acromegaly have typical skin findings including increased sebum secretion, decreased transsudial water loss, more alkaline, and colder skin surface correlated with serum GH and IGF1 levels. The aim of this study was to demonstrate the effect of functional skin changes on the skin flora in patients with acromegaly.

Methods and designs
This case–control study was conducted in university hospitals in Mersin, Turkey. study consisted of 30 acromegalic patients and 60 healthy adults who had no previous diagnosis of chronic illness as a control group. A total of 90 volunteers were enrolled in a cohort: nasal and axillar cultures were obtained. Axillar and nasal specimens from anterior nares of the individuals were taken using sterile swabs.

Results
Nasal colonization of Staphylococcus aureus was 13.3% in acromegalic patients, but 43.4% in control group this differences was statistically significant (P=0.004). Patients and control group compared according to axillar and nasal cultures, we determined proteins colisation 16.7% in patients with acromegaly but no proteins colisation in control group. This result was statistically significant (P=0.001). Proteus colonization was negatively correlated only with disease duration in acromegalic patients (P=0.017).

Conclusion
Nasal colonization with Proteus vulgaris seems to be a marker of disease duration in acromegalic patients.

DOI: 10.1530/endoabs.32.P916

P917
Effect of short- and long-term treatment with pasireotide on hemochrome in patients with Cushings’s disease
Alessia Cozzolino1, Chiara Simeoli1, Laura Trentimonti2, Monica De Leo3, Pasquale Vitale1, Davide Lucanelli1, Aurora Albano1, Marco Boscaro1, Annamaria Colao1, Giorgio Arnaldi2 & Rosario Pivonello2
1Section of Endocrinology, Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy; 2Division of Endocrinology, Politecnico University of Marche, Ancona, Italy.

Introduction
Glucocorticoids (GC) have a stimulatory effect on neutrophils and an inhibitory effect on the other leukocyte subpopulations. A potential stimulatory effect on erythropoesis has been also hypothesized. The aim of our study was to evaluate the effect of pasireotide treatment on hemochrome parameters in patients with endogenous pituitary-dependent glucocorticoid excess or Cushings’s disease (CD).

Patients and methods
Fifteen patients with CD (19–57 years, 14 F, 1 M) and 45 sex-, age- and BMI-matched healthy controls entered the study. Hemochromate evaluation has been assessed at baseline and after 3 and 6 months of pasireotide treatment (dose 1200–2400 ng/day).

Results
Significantly higher levels of hematorcit (HCT) (P=0.019) and neutrophils (P=0.002) and a significantly lower number of lymphocytes (P=0.000) and eosinophils (P=0.009) have been observed in patients than controls. After 3 months of treatment, 8/15 patients (53.3%) normalized urinary free cortisol
Evaluation of QT dispersion at the time of diagnosis and at the end of follow-up in acromegaly patients

Husniye Baser1, Nihal Akar Bayram 2, Burcak Polat1, Berna Evrenos1, Reyhan Ersoy1, Engin Bozkurt* & Bekir Cakir1
1Department of Endocrinology and Metabolism, Ataturk Education and Research Hospital, Ankara, Turkey; 2Department of Cardiology, Ataturk Education and Research Hospital, Ankara, Turkey.

Background

In this study we have aimed to calculate the QT dispersion in acromegaly patients and reveal its correlation with GH and IGF1.

Materials and methods

Forty-one acromegaly patients were enrolled in the study. Another 41 patients with similar age, sex and comorbid disease distribution have constituted the control group. We have evaluated the electrocardiograms (ECG) of the acromegaly patients at the time of diagnosis (baseline) and at the end of follow-up (post follow-up). Only one ECG was provided from each patient in the control group. The longest (QT max), the shortest QT (QT min), QT dispersion, corrected QT max (QTc max), QTc min and QTc dispersion were calculated.

Results

Baseline QT max, QT dispersion, QTc max and QTc dispersion intervals were significantly longer than the control group (respectively; P = 0.016, P = 0.001, P = 0.001, P = 0.002). QTc max and QTc dispersion intervals were significantly shorter at the end of the follow-up period compared to baseline, in acromegaly patients (respectively; P = 0.005, P = 0.024). Post follow-up QT intervals were not statistically different from the control group. Except the negative correlation between GH and QTc dispersion of acromegaly patients in post follow-up period, we could not detect any other correlation between QT intervals and GH or IGF1 levels. QTc dispersion was found to be related with disease duration in acromegaly group (r = 0.440, P = 0.009).

Conclusions

According to the findings of this study we can claim that QT intervals are beneficial in determining the arrhythmia risk in acromegaly patients and this risk can be reduced after treatment and hormonal control.

DOI: 10.1530/endoabs.32.P919

Transsphenoidal surgery, gamma-knife surgery and diabetes are the factors affecting the quality of life in acromegalic patients

Ayse Serap Yalın, Sedu Sancak, Oğuzhan Deyneli, Mutlu Gunes, Sule Temizkan, Dilek Gogas Yavuz & N. Sema Akalin

Section of Endocrinology and Metabolism, Department of Internal Medicine, School of Medicine, Marmara University, Istanbul, Turkey.

Acromegaly is a chronic disease with an important impact on patients, health-related quality of life (HRQoL). Acromegaly quality of life questionnaire (AcroQol) is a disease-generated Qol questionnaire comprising 22 questions each having five possible responses scored 1–5, the maximum score of 110 reflecting best possible QOL, and quoted as a percentage. The 22 items break down into two categories, physical and psychological function, the latter being subdivided into appearance and personal relationships. We aimed to investigate the factors affecting the QoL in acromegalic patients by using AcroQol. We have performed a cross-sectional study in 65 acromegalic patients (37 males, 28 females). Age (mean ± s.d.: 44.75 ± 10.81 years), BMI (mean ± s.d.: 29.77 ± 4.20 kg/m²), disease duration (median (IQR): 48 (12–103) months), basal GH (median (IQR): 1.66 (0.69–6.05) ng/dl), nadir GH (median (IQR): 1.13 (0.47–4.80) ng/dl), and IGF1 (median (IQR): 311 (199–504.5) ng/dl) were evaluated. Comorbidities were as follows: diabetes 27.7%, hypertension 43.1%, hyperlipidemia 32.3%, and hypopituitarism 29.2%. 55 patients (84.6%) underwent transphenoidal surgery (TSS), gamma-knife radiosurgery (GKS) was performed in 39 (60%) patients and 41 (63.1%) patients were on somatostatin analogue (SA) treatment. Disease control was evaluated by IGF1 (reference values per age) and GH levels (random GH <1 ng/dl in patients on SA and nadir GH <0.4 ng/dl in patients not on SA); 24 (36.9%) patients were under control according to IGF1 criteria, while 20 (30.8%) patients were under control according to GH criteria. No correlation was found between AcroQol scores and any of the parameters. AcroQol scores were lower in patients with diabetes (52 vs 67, P < 0.05) and who had radiotherapy (59 vs 75, P < 0.05). However, patients who underwent TSS had higher scores (66 vs 39, P < 0.05). In conclusion, TSS, GKS and co-existing diabetes were the only factors affecting acromegaly related QoL.

DOI: 10.1530/endoabs.32.P919

The short synacthen test may be more sensitive than the glucagon stimulation test in assessing the hypothalamic–pituitary–adrenal axis: a retrospective audit

Richard Blythe, Ismail Elkahsi & Mohamed Malik

Scunthorpe General Hospital, Scunthorpe, UK.

Introduction

Insulin tolerance test (ITT) is considered as the gold standard assessment for hypothalamic-pituitary–adrenal axis (HPA) integrity. Short synacthen test (SST) is a relatively simple, low-cost and well tolerated first line test of HPA despite concerns regarding accuracy. The glucagon stimulation test (GST) is often used as an alternative to the ITT. Although less reliable, it is particularly useful when insulin-induced hypoglycaemia is contraindicated. This retrospective audit set to evaluate accuracy of the SST and GST against the ITT with the aim of advising on the best method of HPA investigation.

Method

Patients who underwent ITT between 2009 and 2012 and had at least one screening test were audited. The ITT was considered as gold standard and pre-screening SST and/or GST results were compared against it. Results

31 patients underwent ITT of whom 31 had pre-screening SST and/or GST. 21 were females and average age was 42.9. 23 with clinically suspected hypopituitarism; six post-transphenoidal surgery and two with non ACTH-producing pituitary adenoma. 31 of the 31 patients underwent both SST and ITT. 13 patients failed both SST and ITT and only one patient passed SST but failed ITT giving an SST sensitivity of 92.8% (95% CI 86.1–99%) and a specificity of 8.3% (95% CI 4–16.2%). Six out of 16 patients underwent both GST and ITT failed both tests, while two passed GST but failed ITT giving GST sensitivity of 75% (95% CI 75–94.7%) and a specificity of 0% (95% CI 0–19.7%). Measure of agreement between SST and GST was poor (κ = 0.13).

Conclusion

SST is more sensitive and specific than GST for assessing HPA when compared to the gold standard ITT.

Recommendation

SST is a more appropriate screening test for HPA axis and should replace the GST when ITT is contraindicated.

DOI: 10.1530/endoabs.32.P920

Abstract withdrawn.
Characterization of GH-producing pituitary adenomas according to responsiveness to thyrotropin-releasing hormone

Sang Ouk Chin & Sung-Woon Kim
Department of Endocrinology and Metabolism, Kyung Hee University School of Medicine, Seoul, Republic of Korea.

Objective
The relationship between the paradoxical response of GH secretion after thyrotropin-releasing hormone (TRH) administration and tumor size has been the subject of only a few studies with conflicting results.

Design
The aim of this study was to investigate how the paradoxical response of GH secretion to TRH changes according to tumor size.

Methods
Patients with newly diagnosed acromegaly were classified as either TRH responders or non-responders according to the results of a TRH stimulation test (TST). GH levels of patients during the TST were compared according to responsiveness to TRH and tumor size. The relationship between ΔGHmax→min (the difference between peak and basal GH levels during the TST) and tumor size was investigated. Lastly, tumor volumes were compared between TRH responders and non-responders.

Results
A total of 112 acromegalic patients who underwent the TST were included in this study. TRH responders showed significantly higher GH levels than non-responders during the entire TST time. ΔGHmax→min during the TST was higher in TRH responders than non-responders, and tumor volumes were likely to be greater in responders than non-responders, although this difference was not statistically significant. Among 69 patients who remained after excluding patients without results of other tests or sellar MR images, those with macroadenomas greater in responders than non-responders, although this difference was not statistically significant. Among 69 patients who remained after excluding patients without results of other tests or sellar MR images, those with macroadenomas demonstrated higher GH levels during the entire TST time. Both peak GH levels and ΔGHmax→min during the TST showed significant correlations with tumor volume.

Conclusion
The paradoxical response of GH secretion to TRH in GH-producing pituitary adenomas was positively correlated with tumor size.

DOI: 10.1530/endoabs.32.P922

P924
Endoscopic transsphenoidal surgery for acromegaly: assessing the surgical outcome based on current criteria of remission

Grzegorz Zielinski¹, Przemyslaw Witek¹ & Jan Podgorski²
¹Department of Neurosurgery, Military Institute of Medicine, Warsaw, Poland; ²Department of Endocrinology and Isotope Therapy, Military Institute of Medicine, Warsaw, Poland.

Introduction
Acromegaly is associated with increased morbidity and mortality, mainly due to cardiovascular and metabolic complications and higher risk of malignancy. The treatment of choice is selective transphenoidal surgery (TSS). Successful removal of somatotroph adenoma normalizes GH and IGF1 levels, which improves the patients prognosis. The efficacy of TSS depends on the tumor volume, parasellar extension and surgeon experience.

The aim of this study was to assess the safety and efficacy of pure, endoscopic TSS based on the stringent criteria of remission.

Material and methods
Retrospective study involving 25 consecutive patients with GH-secreting pituitary adenoma (9 males and 16 females). The mean age was 45.04 years. All subjects underwent pure endoscopic TSS in 2010. They were all operated on by the same neurosurgeon and according to the same surgical protocol. Diagnosis of acromegaly was based on commonly adopted hormonal criteria and magnetic resonance imaging (MRI). Lateral invasion to the cavernous sinuses was classified according to Knosp’s scale. Remission was defined as nadir GH ≤ 0.4 mg/ml following 75.0 mg of oral glucose and IGF1 within the referral limits for age and gender or random GH ≤ 1 mg/ml.

Results
The MRI precisely visualized 18 macroadenomas (72%) and 7 microadenomas (28%) in the study group. Remission was achieved in 11 subjects with macroadenomas (61.1%) and in six patients with microadenomas (85.7%). Intraoperative, cerebrospinal fluid leakage was observed in six subjects with pituitary macroadenoma. Additionally, one case of epistaxis and one sinusitis was found. There were neither meningitis nor persistent CSF leakage. The permanent diabetes insipidus and anterior pituitary insufficiency was observed in case of one patient.

Conclusions
Pure endoscopic TSS was an effective and safe procedure. The main limitation of complete tumor removal was cavernous sinuses involvement.

DOI: 10.1530/endoabs.32.P924

P925
The influence of octreotide-LAR treatment on glucose homeostasis in acromegaly

Maria Stelmachowska-Banas, Piotr Zdunowski & Wojciech Zgliczynski
The Centre of Postgraduate Medical Education, Warsaw, Poland.

Introduction
Impaired glucose tolerance and insulin resistance are frequently associated with acromegaly. The aim of this study was to assess the effect of octreotide-LAR treatment on glucose homeostasis in acromegalic patients.

Patients and methods
In this prospective study 16 naïve acromegalic patients were studied before and after 3-month therapy of octreotide-LAR (20 mg i.m. every 28 days). Diagnosis of active acromegaly was established on the basis of widely recognized criteria. In each patient glucose and insulin concentrations were assessed during the 75 g oral glucose tolerance test (OGTT) and HbA1c levels were measured. To estimate insulin sensitivity hyperinsulinemic euglycemic clamp method was used and homeostasis model assessment (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) were calculated.

Conclusions
In patients with newly-diagnosed GH-secreting pituitary macroadenoma, primary therapy with lanreotide Autogel at 120 mg every 28 days achieved clinically-relevant reduction in pituitary adenoma volume and sustained GH/IGF1 control with a favourable safety profile over 48 weeks’ follow-up. These data support further exploring the potential use of lanreotide as an initial therapeutic option in this patient population.

DOI: 10.1530/endoabs.32.P925
Results
After 3 months of treatment no statistically significant change in plasma glucose levels both fasting and during OGTT (P > 0.05) was found, but a significant reduction in HbA1c level (6.54 ± 1.72% vs 6.02 ± 0.78%) was noticed. A prominent reduction in insulin secretion was found after octreotide-LAR treatment compared to the moment of diagnosis (4.4 ± 2.0 vs 12.1 ± 9.6 mIU/mL, P < 0.001). After treatment, there was a significant reduction in HOMA-IR (0.92 vs 2.27, P < 0.05) and a significant increase in QUICKI (0.39 vs 0.34, P < 0.05). In euglycemic clamp method a statistically significant increase in M value (4.52 ± 2.34 vs 2.37 ± 1.24 mg/kg per min) was noticed.

Conclusions
We concluded that in acromegalic patients octreotide-LAR therapy significantly improves glucose homeostasis by reducing insulin resistance.

DOI: 10.1530/endoabs.32.P925

P926
Somatotropin and IGF1 levels at diagnosis and after surgery in acromegalic patients: is it possible to predict the likelihood of cure at diagnosis?
Sandra Belo1,3, Cláudia Nogueira1,3, Angela Magalhaes1,3, Eduardo Vinha1, Joana Pereira2 & Davide Carvalho1,3
1Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar de São João, Porto, Portugal; 2Department of Neurosurgery, Centro Hospitalar de São João, Porto, Portugal; 3Faculty of Medicine, University of Porto, Porto, Portugal.

Introduction
Elevated levels of somatotropin (ST) and IGF1 in acromegalic patients are associated with high morbidity and mortality. The normalization of ST and IGF1 allows the reversal of most of their negative effects.

Objective
To evaluate characteristics present at diagnosis, predictive of cure, after surgery, in patients with ST-producing tumors.

Methods
Retrospective study including acromegalic patients diagnosed between 1982 and 2012. Patients that underwent surgery and postoperative evaluation were selected. Data regarding tumor characteristics, ST nadir, IGF1 levels and clinical parameters was collected. Independent samples t-test and partial correlation were used for statistical analysis.

Results
We evaluated 47 patients with ST-producing tumors. Mean age at diagnosis was 42.0 ± 12.4 years, delay in diagnosis 6.0 ± 4.4 years, tumor size (considering the largest diameter) 18.7 ± 12.6 mm, ST nadir, prior to surgery, 19.2 ± 24.3 mg/mL, and after surgery 5.1 ± 12.0 mg/L. Patients with cure criteria after surgery were compared with patients with persistent disease (ST nadir after surgery 0.39 ± 0.36 vs 10.24 ± 16.78 mg/mL, P = 0.025). No differences were found between the two groups relating the delay in diagnosis (6.1 ± 5.1 vs 6.1 ± 4.4 years, P = 0.985), prolactin levels (44.2 ± 98.1 vs 45.9 ± 52.3 mg/mL, P = 0.946), IGF1 (807.3 ± 344.9 vs 744.4 ± 323.4 mg/mL, P = 0.576) and tumor size (18.6 ± 14.1 vs 18.7 ± 8.7 mm, P = 0.982). Differences were found regarding age at diagnosis (48.2 ± 14.3 vs 40.0 ± 9.3 years, P = 0.04) and ST nadir before surgery (10.8 ± 9.4 vs 21.9 ± 19.2, P = 0.047), this with moderate correlation with postoperative nadir (r = 0.415, P = 0.008), after controlling for age. There were no differences in the frequency of symptoms and manifestations of the disease between the two groups.

Discussion
Higher levels of ST nadir at diagnostic OGTT confer greater risk of persistent disease after surgery.

DOI: 10.1530/endoabs.32.P926

P927
Therapeutic response to recombinant somatropin in children with isolated deficiency of GH
Sandra Belo1,3, Cláudia Nogueira1,3, Susana Corujeira2, Carla Costa2,3, Cintia Castro-Correia2 & Manuel Fontoura1,3
1Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar de São João, Porto, Portugal; 2Department of Pediatrics, Centro Hospitalar de São João, Porto, Portugal; 3Faculty of Medicine, University of Porto, Porto, Portugal.

Introduction
Treatment with recombinant ST is subject to strict criteria. Differences in the response to therapy based on the maximum level of ST in diagnostic tests (ST ≤ 5 vs ST > 5 ng/mL), could predict whose patients would benefit more from therapy.

Purpose
Assess differences in the response to therapy with rST in patients with IDGH.

Methods
Selected 18 patients with IDGH followed by Endocrinology. Anthropometric (height (H), weight, growth velocity (GV), target height (TH)), analytical (IGF1, IGFBP3) and imaging (bone age (BA)) data were collected before, and 12 months after treatment. Two groups were formed in ST levels obtained in the stimulation tests, ST ≤ 5 ng/mL (n = 9) and ST > 5 ng/mL.

Results
The sample (male n = 13) presented chronological age (CA) of 8.6 ± 3.5 years, ST 114.3 ± 21.6 cm (z-score = 2.7 ± 0.6), BMI 17.3 ± 3.1 kg/m², TH 165.4 ± 7.3 cm; BA: 5.8 ± 3.5 years; GV: 4.0 ± 0.8 cm/year; IGF1 104.1 ± 93.6 ng/mL, IGFBP3 2.8 ± 1.3 mg/mL. After 12 months of therapy there was a significant increase in GV (8.1 ± 2.0, P < 0.001) and H (123.9 ± 19.2, P < 0.001; z-score = 2.0 ± 0.9). When comparing both groups, there was a difference in ST levels after stimulation tests (3.4 ± 1.8 vs 5.9 ± 1.1 ng/mL, P = 0.03). There were no other differences between the two groups when comparing for dose of rST (0.035 ± 0.008 vs 0.035 ± 0.005 mg/kg per day, P = 0.867), anthropometric (H 114.4 ± 21.2 vs 114.1 ± 16.9 cm, P = 0.98; GV 3.8 ± 0.7 vs 4.2 ± 0.9 cm/year, P = 0.28), analytical (IGF1 104.1 ± 77.1 vs 103.3 ± 68.1 ng/mL, P = 0.07) or imaging (BA 5.9 ± 3.9 vs 5.7 ± 3.2 years; P = 0.90) parameters before treatment. The same was observed 12 months after therapy (ST dose 0.031 ± 0.008 vs 0.029 ± 0.004 mg/kg per day, P = 0.42; H 124.4 ± 22.2 vs 123.5 ± 16.6 cm, P = 0.93; GV 8.5 ± 2.5 vs 7.7 ± 1.4 cm/year, P = 0.44; IGF1 258.8 ± 243.4 vs 309.0 ± 191.4 ng/mL, P = 0.63).

Conclusion
Response to therapy with rST in children with IDGH is similar in cases of severe and in cases of partial deficit.

DOI: 10.1530/endoabs.32.P927

P928
Thyroid cancer in patients with acromegaly
Inga Balciene1, Raitis Peculis1,3, Janis Klovins1,2 & Valdis Pirkstis1,3
1Pauls Stradins Clinical University Hospital, Riga, Latvia; 2Latvian Biomedical Research and Study Centre, Riga, Latvia; 3University of Latvia, Riga, Latvia.

It is known that acromegaly is associated with increased risk of benign and malignant tumours. Previous studies show the prevalence of nodular thyroid disease in 40–70% of patients with acromegaly, and a 5–7% prevalence of thyroid cancer in these patients, which is higher compared to the general population. Latvian Cancer Register data show an incidence of thyroid cancer of 7.5–7.7 per 100 000 inhabitants in 2007–2010. We retrospectively studied our hospital acromegaly database of 60 patients. Only 10 patients (16%) had nodular goiter, 9 of them underwent thyroid surgery, and in 4 cases (two females and two males) histological examination revealed thyroid cancer (papillary carcinoma in all). It means 6.6% of acromegaly patients had thyroid cancer. Three of four patients with thyroid malignancy, and one of five patients with benign nodules had an active acromegaly at the time of thyroid surgery. Genetic testing of four acromegaly patients with papillary thyroid cancer revealed the presence of SSTR5 gene polymorphism rs3407791T alleles (genotypes TT and TG) in two patients, which is associated with increased risk of acromegaly.

Our results point to a certain association of thyroid cancer with acromegaly activity. The post-operative observation period is too short to allow evaluation of the rate of possible thyroid cancer relapse, especially in patients with consistently increased GH and IGF1. Patients with acromegaly and nodular goiter should be often controlled by thyroid ultrasound followed by fine needle aspiration biopsy as indicated.

DOI: 10.1530/endoabs.32.P928

P929
Therapeutic role of dopamine-agonists in ESRF-induced hyperprolactinaemia
Sajini Wijetilleke1, Chandra Parvathy1, Arla Ogilvie1 & Chantal Kong1,2
1Watford General Hospital, Watford, UK; 2St Albans City Hospital, Hertfordshire, UK.

Moderate hyperprolactinaemia (<1000 mU/l) is a common abnormal biochemical finding in patients with end-stage renal failure (ESRF). The underlying
pathophysiological mechanism is thought to be due to a combination of increased prolactin secretion as well as delayed renal clearance. There are no current clear guidelines for the treatment of ESRF-induced symptomatic hyperprolactinaemia but renal transplantation has been shown to reverse the raised prolactin back to normal. We describe two cases whereby dopamine-agonist treatment induced regression of prolactin-related signs and symptoms in ESRF. A 69-year-old man with a history of ESRF due to focal segmental glomerulosclerosis on haemodialysis presented with bilateral gynaecomastia and his pituitary stalk. He was commenced on Bromocriptine which normalised his prolactin and he improved symptomatically. His serum testosterone however remained low.

CT pituitary findings remained unchanged however. A 53-year-old man on haemodialysis for ESRF secondary to resistant hypertension complained of reduced libido, erectile dysfunction and painful bilateral gynaecomastia. Investigations showed a low testosterone level of 6.3 nmol/l with an elevated prolactin levels of 2683 mU/l which was initially thought to be secondary to ESRF. MRI of his pituitary showed a thickened pituitary stalk. He was commenced on Bromocriptine which normalised his prolactin and he improved symptomatically. His serum testosterone however remained low.

These cases illustrate that dopamine agonists clearly have a therapeutic benefit in ESRF-induced hyperprolactinaemic breast symptoms and should be considered as a potential useful medical therapy target. They do not however seem to improve hypogonadism. This would suggest a different mechanism affecting disturbance of the neuroendocrine hypogonadal system by ESRF.

P930

A rare case of pituitary infarction in an 11-year-old pre-pubertal girl with pituitary autoantibodies to piccolo

Patricia Crock1, Vicki Maltby1, Casey J A Smith1,4, Sophie Bensing2, Dieter K Ludecke1 & Olle Kämpe1

1University of Newcastle, Newcastle, New South Wales, Australia; 2Endocrinology and Diabetology Unit, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milan, Italy; 3Division of Endocrinology and Diabetology, Department of Internal Medicine, Kantonsspital St Gallen, St Gallen, Switzerland; 4Division of Endocrinology, Spital Grabs, Grabs, Switzerland; 5Department of Internal Medicine, Spital Wattwil, Wattwil, Switzerland.

Introduction

Pituitary infarction is rare in the paediatric age. In adolescents and adults it is a potential secondary to haemorrhage into an underlying lesion such as pituitary adenoma or cyst. Lymphocytic hypophysitis is rare in children and usually peri-tumoral due to germinoma, craniopharyngioma or Rathke’s cyst and often associated with hypopituitarism and diabetes insipidus. Case report

An 11-year-old girl was admitted with a urinary tract infection (UTI) and sudden onset vomiting. She also had experienced frontal headaches, fever, low blood pressure, lethargy and 6 kg weight loss of 3 weeks duration. Symptoms seemed disproportionate to a UTI alone. Laboratory tests indicated normal electrolytes but low TSH 0.09 mIU/l (0.6–3.7) and morning cortisol 30 nmol/l (15–500). All patients reported longstanding (1–10 years) fatigue and weakness retrospectively. Relapsing hypopituitarism had been previously documented in one patient. The further workup did not reveal deficiencies of other pituitary hormones and sellar MRI scans were normal in two patients and showed a partially empty sella in the remaining. Hydrocortisone replacement resulted in rapid resolution of hypopituitarism and clinical improvement in every patient.

Conclusion

Secondary adrenal insufficiency due to isolated ACTH deficiency, although rare, must be included in the differential diagnosis of hypopituitarism. Enhanced vasopressin release due to a lack of cortisol mediated negative feedback suppression is the likely pathogenetic mechanism leading to euvolemic hypopituitarism. Associated autoimmune diseases may point to the underlying mechanism of corticotroph dysfunction but the etiology may remain obscure despite extensive workup. Hydrocortisone replacement results in rapid clinical and biochemical improvement and should promptly be installed.

P931

Idiopathic isolated ACTH deficiency presenting with severe hyponatraemia

Tilman Drescher1, Christoph Ackermann2, Irene Bätcher3, Ina Krull1, Michael Brändle1 & Stefan Bila1

1Division of Endocrinology and Diabetes, Department of Internal Medicine, Kantonsspital St Gallen, St Gallen, Switzerland; 2Department of Internal Medicine, Spital Grabs, Grabs, Switzerland; 3Department of Internal Medicine, Spital Wattwil, Wattwil, Switzerland.

Introduction

Acromegaly is a rare and insidious disease associated with an increased morbidity and mortality. Trans-sphenoidal (TNS) surgery remains the primary therapeutic option, in particular for intrasellar microadenomas and noninvasive macroadenomas. Aims of this study were to describe diagnostic features and to verify the impact of TNS surgery on treatment of acromegaly over three decades, before and after the identification of a dedicated neurosurgical team. Design and methods

Forty-nine patients (group A) who underwent TNS surgery by a dedicated neurosurgical team between 2000 and 2010, and 126 patients (group B) who underwent TNS surgery by a not selected operator between 1979 and 1999 were retrospectively analyzed.

Results

At baseline, 67% of patients of group A and 69% of patients of group B were macroadenomas. The mean delay of diagnosis was 5.5 and 5.9 years in group A and
Predictors of hormonal status after pituitary surgery

Objective
To evaluate the frequency of hypopituitarism and investigate the potential predictors of worsening or improving pituitary function after PA surgery.

Methods
Retrospective analysis of all PA operated in our hospital between 2001 and 2010.

Results
Eighty patients were included (51.2% women), with a mean age of 55.6 years (s.d. 16.6 years); 71.2% had non functioning PA, 95% were macroadenomas and mean tumor size was 25.8 mm (s.d. 14 mm). Preoperative hormonal status was normal in 45.3%, 18.8% had 1–2 pituitary deficits and 35.9% had ≥3 deficits. After the intervention, pituitary function was improved or no changed in 70.4% of patients (41.8% had a normal function, 20% 1–2 deficits and 38.2% ≥3 deficits).

Predictors of hormone impairment: on univariate analysis we found a non significant trend to worsening in macroadenomas, PA with extrasellar extension and patients with postoperative cerebrospinal fluid fistula. In the last 5 years, the percentage of hormone impairment was reduced (44.4 vs 19.2%, \( P = 0.07 \)).

Conclusions
Tumor size and invasion were significant and independently associated to TSH, GH and FSH/LH postsurgical deficits. A normal basal pituitary function was the main conditioning of a normal postsurgical pituitary status. The 85.7% of patients with normal postoperative function had a normal preoperative function too (\( P < 0.001 \)).

On multivariate analysis with logistic regression, size, PA functionality and the number of presurgical deficits were predictors of hormone improving. On the other hand, surgery in the first 5 years of the study period was related to hormone impairment.

Introduction
Epilepsy is a heterogeneous condition with different aetiologies including genetics, cerebral trauma, toxic exposures, infection, vascular diseases and neoplasms. Among the last ones, pituitary tumours (PT) are rarely responsible of convulsions, except when they are very large invading the nervous system. Our aim is to analyze the conditions under which the epilepsy appears and disappears in people with pituitary tumours.

Subjects and methods
We have analyzed eight subjects who were hospitalized in our department for pituitary tumours and epilepsy. After questioning them, they were examined, and then had biological, hormonal and radiological assessment based on MRI. Among this group we had six pure PRL, one adenoma secreting prolactin and GH and the 8th one was a non functioning pituitary tumour. Chronic epileptic crisis was the consultation motive in 7/8 cases although there were other symptoms such as visual and sexual troubles. In one case acute epileptic crisis appears during radiotherapy. All were males, mean age = 33.75 years (22–58), mean prolactin = 9198 ng/ml and tumour’s height was >40 mm in all except one. The temporal lobe was invaded in six cases. After tumour volume reduction (by surgery \( n = 1 \), medications \( n = 7 \)), epilepsy disappeared and epileptic drugs were stopped except in one recent case.

Conclusion
Epilepsy which is a life threatening condition can reveal some pituitary tumours, especially large somatotrophic or pure prolactinomas. It can also appear under aggressive treatment such as radiotherapy. That one should be avoided before tumour reduction by surgery or medical treatment if possible.

DOI: 10.1530/endoabs.32.P934

Predictors of hormonal status after pituitary surgery

Rocío Villar Tabo1, Alfonso Vidal Casarejo2, María D Ballesteros Pomar2, Rosa Álvarez San Martín2, Javier Fernández Fernández2, Teresa Ribas Artilio2, Elena Galán Rusueña2 & Hiduro Cano Rodríguez3
1Endocrinology and Nutrition Department, Complejo Asistencial Universitario de León, León, Spain; 2Neurosurgery Department, Complejo Asistencial Universitario de León, León, Spain; 3Pathology Department, Complejo Asistencial Universitario de León, León, Spain.

Introduction
Surgical treatment of pituitary adenomas (PA) may affect hormone situation.

and B, respectively. Moreover, no significant differences between two groups in terms of mean basal GH levels, mean GH nadir values, prevalence of hypopituitarism and hypertension were observed. IGF1 SDS were significantly higher, while BMI and prevalence of IGT/diabetes were significantly lower in group B than in group A. After surgery, overall remission rate was 53% in patients of group A (75% in microadenomas and 42% in macroadenomas, \( P < 0.05 \)) and 37% in patients of group B (\( P = 0.08 \) vs group A; for microadenomas, 34 vs 75% of group A, \( P < 0.05 \), for macroadenomas, 36 vs 42% of group A, \( P = NS \)).

Conclusions
Our data confirm that a dedicated neurosurgical team is needed in order to improve remission rates of surgery in acromegalic patients. However, we do not observe significant changes in biochemical, clinical and neuroradiological presentation of disease over the last three decades. As the high prevalence of macroadenomas negatively influence surgical cure, earlier diagnosis should be considered mandatory to achieve a better outcome.

DOI: 10.1530/endoabs.32.P932

Pituitary tumours and epilepsy

Lina Akkache, Katia Dafleur & Farida Chentli
Department of Endocrine and Metabolic Diseases, Bab Oued Hospital, Algiers, Algeria.

Introduction
Epilepsy is a heterogeneous condition with different aetiologies including genetics, cerebral trauma, toxic exposures, infection, vascular diseases and neoplasms. Among the last ones, pituitary tumours (PT) are rarely responsible of convulsions, except when they are very large invading the nervous system. Our aim is to analyze the conditions under which the epilepsy appears and disappears in people with pituitary tumours.

Subjects and methods
We have analyzed eight subjects who were hospitalized in our department for pituitary tumours and epilepsy. After questioning them, they were examined, and then had biological, hormonal and radiological assessment based on MRI. Among this group we had six pure PRL, one adenoma secreting prolactin and GH and the 8th one was a non functioning pituitary tumour. Chronic epileptic crisis was the consultation motive in 7/8 cases although there were other symptoms such as visual and sexual troubles. In one case acute epileptic crisis appears during radiotherapy. All were males, mean age = 33.75 years (22–58), mean prolactin = 9198 ng/ml and tumour’s height was >40 mm in all except one. The temporal lobe was invaded in six cases. After tumour volume reduction (by surgery \( n = 1 \), medications \( n = 7 \)), epilepsy disappeared and epileptic drugs were stopped except in one recent case.

Conclusion
Epilepsy which is a life threatening condition can reveal some pituitary tumours, especially large somatotrophic or pure prolactinomas. It can also appear under aggressive treatment such as radiotherapy. That one should be avoided before tumour reduction by surgery or medical treatment if possible.

DOI: 10.1530/endoabs.32.P933

Fetuin-A can be used as a marker of acromegaly

Senay Topsakal1, Fulya Akin2, Guzin Yaylali1, Sebahat Turgut3, Duygu Herek3, Emrah Yerlikaya1 & Ceylan Ayada2
1Department of Endocrinology, Pamukkale University, Denizli, Turkey; 2Department of Physiology, Pamukkale University, Denizli, Turkey; 3Department of Radiology, Pamukkale University, Denizli, Turkey.

Introduction
Acromegaly is a rare, chronic disorder, with classical clinical features caused by excess GH and consequent raised levels IGF1 and is associated with increased morbidity and mortality. Early diagnosis of the disease is very important for patient survival. Fetuin-A is a plasma glycoprotein that is produced by hepatocytes and it is the most important systemic calcification inhibitor. The physiological importance of fetuin-A, in acromegaly remains obscure. The aim of this study was to investigate the effect of fetuin-A levels on atherosclerotic process in acromegalic patients.

Methods
In this study 37 acromegalic patients and 30 controls were included to the study. Anthropometric, biochemical and hematological findings were examined. Height, weight, BMI, and blood pressure of the groups were noted. Fasting blood glucose, lipid profile, GH, IGF1, IGFBP3, TSH, insulin levels were measured. Fetuin-A levels were measured by Elisa method.

Results
We observed significantly higher Fetuin-A levels in acromegalic patients (\( P < 0.001 \)). There was no correlation between Fetuin-A and GH, IGFBP3, HOMA, BMI, TG, T. col, HDL and LDL levels. It was found positive correlation between Fetuin-A and IGF1 levels (\( P < 0.05 \)).

Conclusion
We observed significantly higher fetuin-A levels in acromegalic patients. Our study was the first study that evaluates fetuin-A levels in acromegalic patients. We found positive correlation with fetuin-A and IGF1, in acromegalic patients.

DOI: 10.1530/endoabs.32.P935
Introduction
The effects of hyperprolactinemia on metabolic parameters are not conclusive and a few data evaluating adiponectin levels in prolactinoma and idiopathic hyperprolactinemia exist. The aim of this study is to evaluate effects of hyperprolactinemia on body weight, insulin resistance, \( \beta \) cell function, leptin and adiponectin levels in premenopausal women with hyperprolactinemia.

Methods and design
Forty premenopausal women with prolactinoma or idiopathic hyperprolactinemia were compared to 41 age-matched healthy premenopausal women with regard to body weight, BMI, waist and hip circumferences, waist to hip ratio, fasting plasma glucose, insulin, insulin resistance measured by homeostasis model assessment-insulin resistance index (HOMA-IR), \( \beta \) cell function measured by homeostasis model assessment-\( \beta \) index (HOMA-\( \beta \)), leptin and adiponectin levels.

Results
Plasma insulin levels, HOMA-IR and HOMA-\( \beta \) were significantly higher in hyperprolactinemic women than the control group (\( P = 0.012, 0.01 \) and 0.005, respectively). The other parameters were not significantly different from the control group. There was a positive correlation between prolactin levels and fasting plasma glucose (\( P = 0.025, r = 0.354 \)).

Conclusions
The results of the study showed that high prolactin levels may be associated with hyperinsulinemia and insulin resistance in premenopausal women. This effect seems to be independent from body weight, leptin and adiponectin levels. High prolactin levels may directly stimulate insulin secretion from pancreas and directly cause hepatic and whole-body insulin resistance. Correlation between prolactin and fasting plasma glucose suggests an increased hepatic glucose output by prolactin and thus may indicate an increased hepatic insulin resistance.

DOI: 10.1530/endoabs.32.P936

P937
Carbohydrate metabolism in acromegaly and treatment impact
Betina Biagetti, Silvia Valladares, Lorena Arnez, Belen Dalama, Gabriel Obiols & Jordi Mesa, Vall d’Hebron, Barcelona, Spain.

Introduction
Carbohydrate metabolism (CHM) is impaired in over 30% of acromegalic patients. Natural history of acromegaly and treatment modalities, i.e. surgery, somatostatin analogues (SSA) and pegvisomant, may impact in a different way on CHM.

Aim
To assess CHM alterations (impaired fasting glucose (IFG) and diabetes mellitus (DM)) in acromegaly and their relationship with clinical features and treatment options.

Patients and methods
In a retrospective study we have included 55 patients, with acromegaly. Age, gender, BMI, tumor size, IGF1 levels and the presence of IFG or DM have been analyzed before and after surgery or medical treatment.

Results
There were 30 men and 25 women. Mean age before treatment was 57 ± 17 years and mean BMI was 28 ± 3.8 kg/m². We have found IFG in 13 and DM in 15 patients (total 28; 50%). We have found no statistically significant differences in age, gender, BMI and IGF1 levels between IFG/DM and patients without CHM impairment. However, IFG/DM patients have more frequently macroadenomas. Transsphenoidal resection was performed in 49 (88%) cases. Because of persistence of high postsurgical IGF1 levels (n = 24) or as a primary therapy (n = 6), 30 patients received SSA. For persistence of high IGF1 levels, nine cases were shifted to pegvisomant.

In diabetic patients, HbA1c decreased after surgery from 7.6% (6.7–8.5) to 6.7% (6.2–6.8) and after SSA from 7.1% (6.7–7.4) to 6.6% (5.7–8.5), but only in patients on pegvisomant we have observed a significant reduction HbA1c from (6.2–6.8) and after SSA from 7.1% (6.7–7.4) to 6.6% (5.7–8.5), but only in patients on pegvisomant we have observed a significant reduction HbA1c from 9.8% (8.9–10.5) to 5.6% (5.5–6.8). Furthermore, only in pegvisomant group, we had to lower insulin and/or oral agents whereas with surgery or SSA the diabetic treatment requirement was higher.

Conclusions
Up to 50% of patients with active acromegaly have CHM impairment and correlates with tumor size. Only pegvisomant is associated with significant improvement in glycemic control and a reduction in hypoglycemic treatment. DOI: 10.1530/endoabs.32.P937
Cushing’s disease recurrence after pregnancy
Gizem Fidan Yaylali¹, Fulya Akin¹, Emrah Yerlikaya¹, Senay Topsakal¹ & Duygu Hersek²
¹Department of Endocrinology and Metabolism, Faculty of Medicine, Pamukkale University, Denizli, Turkey; ²Department of Radiology, Faculty of Medicine, Pamukkale University, Denizli, Turkey.

Introduction
Pregnancy is rare in patients with Cushing’s syndrome (CS) because of hypercortisolism, hyperandrogenemia, and/or hyperprolactinemia. Diagnostic tests for CS have become less reliable due to the physiological changes in the hypothalamo-pituitary adrenal (HPA) axis during gestation. Some of these changes may persist until the 5th postpartum week. We report a case of Cushing’s disease (CD) that recurred after pregnancy.

Case presentation
A 32-year-old woman presented with a facial plethora, and menstrual disturbances that had developed over 1 year. Biochemical testing suggested CD. Pituitary MRI demonstrated a macroadenoma extending to suprasellar cysterna with displacement of infundibulum. Transphenoidal surgery was performed. Subsequent biochemical tests suggested remission and her pituitary MRI was normal. This picture continued to be the same during 2 years of follow up. Then, she became pregnant. She presented to endocrinology outpatient clinic at 8 months of pregnancy. She had normal weight gain compatible with her gestation. Her blood pressure and glucose profiles results were also normal. A healthy male infant with normal weight was delivered. At 8 weeks postpartum, she developed facial plethora and began to gain weight. At that time 1 mg dexamethasone suppression test result was 3.3 μg/dl and the basal urinary free cortisol (UFC) was normal. Since it’s immediate postpartum period, we thought that these results still might be persistence of increased maternal (HPA) activity during pregnancy. At 5 months postpartum, she continued to gain weight and there was elevated UFC and loss of diurnal variation of cortisol. Plasma ACTH level was 41.5 pg/ml. Her pituitary MRI revealed 6.5×3.3 mm microadenoma surrounding infundibulum suggesting recurrence. Three months later, her blood pressure began to rise. All clinical and biochemical findings have become overt at that time.

Conclusion
In conclusion, this case illustrates CD can recur after pregnancy and hormonal changes observed during pregnancy make the diagnosis more challenging.

DOI: 10.1530/endoabs.32.P940

Clinical characteristics of patients with congenital hypopituitarism in advanced age
Mirjana Doknic, Sandra Pekic, Dragana Miljic, Marko Stojanovic & Vera Popovic
Clinic of Endocrinology, Diabetes and Metabolic Diseases, Clinical Center Serbia and School of Medicine, University of Belgrade, Serbia, Belgrade, Serbia.

Background
Hypopituitarism is considered to be a risk factor for cardiovascular disease and early death in humans. However, some studies showed that most patients with isolated GH deficiency or combined pituitary hormonal deficiency due to gene mutations (PROP 1, GH receptors gene, GH-1 gene) can survive to advanced age. Aim
To collect clinical data on patients with congenital hypopituitarism older than 50 years identified in the Department of Neuroendocrinology, Belgrade, Serbia between 2005 and 2012.

Patients
Our database contains in total 56 patients with congenital hypopituitarism. Eight of them are older than 50 years (five females and three males, range 53–66 years). Their adult phenotype is typical for childhood onset hypopituitarism, with dwarfism, dry wrinkled skin and lack of sexual development. Their final heights are from 127 to 168 cm and BMI from 16.4 to 31.2 kg/m². According to the number of anterior pituitary hormone deficiencies out of eight elderly patients, five have GHD3 while three patients have GHD2. These patients were not treated with GH, started hormone replacement treatment late in adulthood and were not compliant with the replacement therapy. However, their bone mineral density is not reduced. Glucose metabolism is normal in all and only one patient presented with abnormal lipid profile. They did not have any serious diseases during the life-time. Unfortunately one female and one male patient died due to gastrointestinal bleeding of unknown cause. In most presented patients MRI showed pituitary stalk disconnection and small pituitary.

Conclusion
Our data show that patients with congenital hypopituitarism in advanced age can still have a healthy life style with the absence of cancer, metabolic and cardiovascular diseases.

DOI: 10.1530/endoabs.32.P942
P943
Pituitary abscess after cabergoline treatment of a prolactinoma in a 56 year old male: case report and review of the literature
Benjamin Voelgger¹, Christian Mawrin² & Thomas Schneider¹
¹Klinik fuer Neurochirurgie, Otto-von-Guericke-Universitaet Magdeburg, Magdeburg, Germany; ²Institut fuer Neuropathologie, Otto-von-Guericke-Universitaet Magdeburg, Magdeburg, Germany.

Objective
Abscesses in pituitary adenomas are rare. Continuous progression and haematogenous spread of infections are considered the main pathogenic mechanisms. A standard therapeutic regimen does not exist.

Methods
We report on the case of a 56-year-old male who had been treated with cabergoline for a macroprolactinoma for 4.5 years. The patient presented to our emergency room with sudden deterioration of visual acuity and right oculomotor paresis. A pituitary abscess was identified in MRI, urgently evacuated transphenoidally and then treated with i.v. antibiotics. We provide clinical, histopathological and MRI findings as well as a follow-up at 21 months after surgery. We compare our case to other cases from the literature and, considering the evidence in rodents, discuss potential pathogenic mechanisms with special regard to immunodeficiency.

Results
The favourable result we observed so far as well as the cases reported in the literature warrant to consider urgent transphenoidal evacuation followed by i.v. administration of antibiotics as treatment option of choice in pituitary abscesses. Immune deficiency due to the mass effect of a macroprolactinoma with subsequent suppression of GH secretion and decreased IGF1 release or due to suppression of prolactin-triggered immunomodulation as a side effect of treatment with dopamine agonists have to be taken into consideration as potentially pathogenic mechanisms.

Conclusions
Although pituitary abscesses are rare, neurosurgeons, endocrinologists and ophthalmologists should be aware of this life-threatening entity. Regular follow-up MRI scans in patients treated with dopamine agonists for a prolactinoma are warranted to timely detect signs of potential inflammation. Urgent transsphenoidal evacuation followed by i.v. administration of antibiotics should be considered as treatment option of choice in pituitary abscesses. The function of the immune system in patients with prolactinoma and treated with dopamine agonists should be a matter of further investigations.

DOI: 10.1530/endoabs.32.P943

P944
Tuberculosis: an uncommon cause of hyperprolactinemia
Sunil Kumar Kota¹, Lalit Kumar Meher², Sruti Jammula³ & Kirtikumar D Modi⁴
¹Hospital, Hyderabad, Andhra Pradesh, India; ²MKCG Medical College, Berhampur, Orissa, India; ³Roland Institute of Pharmaceutical Sciences, Berhampur, Orissa, India.

Objective
To report a case of tubercous sclerosis presenting with hyperprolactinemia.

Methods
Clinical, laboratory and radiographic data are reported on a 26-year-old female presenting with galactorrhea and menstrual irregularities.

Case report
A 26-year-old female with no premorbidities presented with complaints of galactorrhea for the past 10 days and menstrual irregularities over the past 6 months. Galactorrhea was spontaneous. Her last childbirth 4 years ago was uneventful. She had no headache, vomiting, and visual impairment. She denied any history of substance abuse, drug intake hypothyroidism, chronic liver or kidney diseases, and epilepsy. She was a well nourished female with mild pallor, tiny nodule on face, subungual fibroma in hands. There was spontaneous galactorrhea and mildly tender breasts without any signs of inflammation. Systemic examination was entirely normal with normal IQ. Ophthalmologic examination revealed, white disk, subretinal hamartoma. Routine laboratory investigations including renal and liver function tests, thyroid profile were normal. Serum prolactin was 85 ng/ml with FSH-4.66 and LH-4.21 mIU/ml. Tests for evaluation of other anterior pituitary hormones were normal. Abdominal and pelvic ultrasound revealed no abnormality. Chest X ray showed bilateral interstitial infiltrates. Echocardiogram of heart was normal. Computed tomography (CT) scan revealed multiple intracerebral calcifications. These calcified lesions subependymal hamartomas are seen along the lateral surface of the lateral ventricles giving rise to characteristic candle dripping appearance.

Conclusion
Tuberous sclerosis: an uncommon cause of hyperprolactinemia

P945
Hemiparesis and hemiplegia as clinical presentation in subjects with pituitary tumours
Meriem Haddad, Katia Daffeur, Nadia Kalafate, Lina Akkache & Farida Chentli
Department of Endocrine and Metabolic Diseases, Bab Oued Hospital, Algiers, Algeria.

Introduction
Pituitary tumours are known to cause headaches and visual troubles by compressing pituitary adjacent structures. Pressure on more distant structures is exceptional. In very large tumours such as prolactinomas, mixed adenomas or craniopharyngiomas, hydrocephalus, convulsions, memory troubles and even unconsciousness can be observed, but to our best knowledge motor deficits, such as hemiparesis or hemiplegia, are rarely reported as clinical presentations in pituitary tumours. Our aim is to report four pituitary tumours with hemi paresis or hemiplegia in order to emphasize the different mechanisms of such neurological troubles.

Case reports
Two men aged 30 and 41, a woman of 26 years old, and a baby aged 5 months were sent for progressive or acute hemiparesis/hemiplegia related to pituitary tumours. In these cases pituitary tumours were all giant (height > 4 cm), invasive (invasion of cavernous sinuses), and compressing distant cerebral structures. After medical treatment, the neurological deficits resolved in subjects with prolactinomas. Unfortunately, the 4th case with craniopharyngioma and active hydrocephalus worsened, and then died.

Conclusion
Although hemi paresis and hemiplegia are very rare clinical presentations in people with pituitary tumours; this aetiology should be kept in mind, as motor deficits can disappear after adequate treatment of pituitary tumours, especially large prolactinomas, as in the reported cases.

DOI: 10.1530/endoabs.32.P945

P946
Relation with carotid intima media thickness and procalcitonin in acromegal patients
Senay Topsakal¹, Fulya Akin¹, Sebahat Turgut², Duygu Herek³, Guzin Yaylali¹, Emrah Yerlikaya¹ & Ceylan Ayuda¹
¹Department of Endocrinology, Pamukkale University, Denizli, Turkey; ²Department of Physiology, Pamukkale University, Denizli, Turkey; ³Department of Radiology, Pamukkale University, Denizli, Turkey.

Introduction
Acromegaly is a rare, insidious, and potentially life-threatening condition. Patients with acromegaly have an increased morbidity and mortality for cardiovascular diseases. However, data on coronary heart disease and atherosclerosis are controversial in patients with acromegaly. Measurement of carotid intima media thickness (cIMT) with carotid doppler ultrasonography is a useful determiner of early atherosclerosis. Procalcitonin is a 116 amino acid peptide with a sequence identical to that of the pro-hormone of calcitonin, but it has no known hormonal activity. Possible relation with high procalcitonin level in acromegaly has been reported.

We aimed to evaluate the any relation with cIMT and procalcitonin levels in acromegaly.

Endocrine Abstracts (2013) Vol 32
Methods
In this study, totally 37 patient (16 patient with cIMT < 0.8; 21 patient with cIMT ≥ 0.8) were used. Thirty age and sex matched healthy controls were included. We measured cIMT and procalcitonin levels. The cIMT measurements were made at the follow-up visit subsequent to when blood samples were obtained. B-mode ultrasonography of the left and right common and internal carotid arteries was performed by a specially trained radiology technician. The common cIMT was calculated as the mean of the left and right measurements and cIMT > 0.8 were evaluated as increased thickness.

Results
We observed higher procalcitonin levels in acromegalic patient with cIMT ≥ 0.8 compared to acromegalic patient with cIMT < 0.8 and results were statistically significant (P<0.05).

Conclusion
Our results showed that procalcitonin can be useful for the assessment of premature atherosclerosis in acromegaly.

DOI: 10.1530/endoabs.32.P946

P947
The role of octreotide LAR treatment on BMI in patients with acromegaly
Zelija Veljia-Asimi
Clinic for Endocrinology and Diabetes, University Clinical Centre of Sarajevo, Sarajevo, Bosnia and Herzegovina.

Objectives
It is known that the obesity and insulin resistance are an integral part of acromegaly. The aim of study was to evaluate the role of octreotide LAR treatment on BMI in patients with acromegaly.

Methods
Sixteen patients with acromegaly diagnosed at Endocrinology Clinic in Sarajevo (10 females and 6 males, mean age 53.4±6.3 years, age range 38–65 years, six patients with microadenoma and 10 patients with macroadenoma) were treated with octreotide. Follow-up period was 3 years (2009–2013). Nine patients were treated with surgical and octreotide treatment. One patient was treated with surgical, octreotide and gamma-knife treatment and six patients were treated only with octreotide LAR. Five patients were diabetics. Anthropometric measurements (including height, weight, BMI and waist), concentration of human GH (hGH), IGF1, CRP, blood glucose, basal insulin and lipid profile were evaluated before treatment and every 6 months during follow-up period of 3 years, while magnetic resonance imaging (MRI) was taken before the treatment and every year during treatment. Thirteen patients received octreotide 30 mg/28 days, one patient received 20 mg and other two 60 mg/28 days.

Results
Octreotide LAR significantly reduced GH (50.13±22.44 vs 21.1±0.56 ng/ml), IGF1 (749.54±112.48 vs 337.33±83.54 ng/ml), adenoma size and CRP (4.56±1.34 vs 2.34±0.01 mg/l) and non-significantly reduced level of basal insulin and cholesterol. During follow-up period octreotide LAR treatment significantly reduced dosage of exogenous insulin at diabetics (~43%). Regression analyses showed inverse association of octreotide treatment and BMI (P<0.001).

Conclusions
Treatment with octreotide LAR in acromegaly significantly reduced BMI, GH, IGF1 and CRP. As well this treatment reduced dosage of exogenous insulin at acromegalic patients with diabetes.

DOI: 10.1530/endoabs.32.P948

P948
Effect of somatotropin and IGF1 secretion on glucose metabolism: diabetic ketoacidosis as first manifestation of acromegaly
Maria Joana Santos1, Rui Almeida2, & Olinda Marques1,2
1Department of Endocrinology, Hospital de Braga, Braga, Portugal; 2Department of Neurosurgery, Hospital de Braga, Braga, Portugal.

Insulin and somatotropin (GH) have opposite effects in glucose metabolism. GH increases the production of glucose through lipolysis and inhibits hepatic and peripheric neoglucogenesis induced by insulin. When insulin secretion is insufficient to overcome insulin resistance, intolerance to glucose or diabetes appears. Drugs used in the treatment of acromegaly also influence glucose metabolism: SSA decrease insulin secretion and pegvisomant has the opposite effect.

The authors present the cases of three male patients, mean age 23.9 years, who were diagnosed with diabetic ketoacidosis (DKA) as first manifestation of acromegaly. No personal or family history of diabetes. All had marked physical features of acromegaly and macroadenomas on MRI. In two patients, initial Hba1c/GH/IGF1 were 9.3%; 155 ng/ml; 458 ng/ml and 11.8%; 229 ng/ml; 1577 ng/ml. They were initially treated with insulin (maximal doses of 0.26 and 1.28 U/kg per day) and metformin 2 g and 3 g/day. No predisposing factor for DKA was identified. They had surgery with partial resection of the adenoma and began treatment with SSA, with marked improvement in glycemic control and progressive reduction of insulin dose, which was suspended 5 and 7 months later. They maintain increased levels of GH and IGF1 and will be treated with surgery and radiosurgery, respectively. The third patient presented with pituitary apoplexy and hypopituitarism at the moment of diagnosis (Hba1c 9.3%; IGF1 38.8 ng/ml). After resolution of DKA, he didn’t temporarily need treatment with anti-diabetic medication. However, 2 months later, he had to start treatment with insulin (Hba1c 12%: IGF1 30 ng/ml). He is currently also being treated with levotyroxine and prednisolone and awaits for surgery. DKA due to relative/absolute insulin deficit is rare as first manifestation of acromegaly (1%). In our series, it represented 6.4% (n=47). The effects of GH and IGF1 on glucose metabolism are complex and could be reversible with the normalization or reduction of GH levels.

DOI: 10.1530/endoabs.32.P949
Diagnosis and treatment of a population of acromegalic patients

Cláudia Nogueira, Sandra Belo, José Pereira, Eduardo Vinha, Angelo Magalhães & Davide Curvahio.
1Centro Hospitalar São João, Porto, Portugal; 2Faculty of Medicine, University of Porto, Porto, Portugal.

Introduction

Acromegaly is a chronic disease caused by GH hypersecretion resulting in increased IGF1 levels. The actions of these hormones result into a broad spectrum of clinical manifestations.

Objective

To evaluate clinical and analytical parameters, imaging, and treatment outcome in a population of acromegalic patients.

Methods

Retrospective study of acromegalic patients diagnosed between 1982 and 2011. Results are presented as mean±S.D.

Results

We included 98 patients (68 women) with a mean age at diagnosis of 45.4±14.6 years and a diagnostic delay of 6.8±5.3 years. Aerial enlargement was the chief complaint (24.5%), followed by headache (18.4%) and maxillofacial changes (14.2%). The most common comorbidities were hypertension (36.7%), carpal tunnel syndrome (34.7%), sleep apnea (26.5%), thyroid nodules (25.5%), impaired glucose tolerance (22.4%) and diabetes (17.3%). Most women (68.6%) reported menstrual disturbances. The majority of tumors were macroadenameas (77.6%) at the time of diagnosis and 36.7% secreted both prolactin and GH. The mean basal GH at diagnosis was 28.5 ng/ml and mean nadir GH achieved during OGTT was 20.8 ng/ml. Gonadotropins deficit was the most common deficit (15 patients), two patients had pan-hypopituitarism, two had combined TSH and gonadotropins deficit and one TSH isolated deficit. The majority of patients (90.8%) were submitted to surgery, mainly by transsphenoidal approach, and cure (biochemical normalization and no recurrence during follow-up) was achieved in 37.1% patients.

Discussion

Although several studies suggest that acromegaly is diagnosed in approximately equal numbers of men and women, in this population there was a higher prevalence of the disease in women, which may reflect a greater concern with body image. The mean age at diagnosis, clinical manifestations and tumor size are similar to those described in other epidemiological studies. We consider a cure rate acceptable considering criteria applied.

DOI: 10.1530/endoabs.32.P950

Syndrome of inappropriate antidiuresis due to low dose hydrochlorothiazide use in a patient after transsphenoidal surgery for pituitary adenoma

Daria Mikhailyova, Svetlana Vorotnikova, Ekaterina Pigarova, Andrey Grigor’ev & Larisa Dzeranova
Endocrinology Research Centre, Moscow, Russia.

Introduction

Hyponatremia is one of severe postoperative water-electrolyte disturbances. This condition is usually caused by syndrome of inappropriate secretion of antidiuretic hormone or cerebral salt-wasting syndrome which require different treatment approaches.

Case presentation

A 61-year-old woman was referred to tertiary care center with non-functioning adenoma and had been treated with antihypertensive therapy that included ACE inhibitors and 12.5 mg of hydrochlorothiazide for several years. Macroadenoma was detected 2 years ago and in 2012 the MRI showed rapid suprasellar tumor growth.

At presentation

TSH 0.43 mIU/ml (0.25–3.5), FT4 15.31 pmol/l (9–20), ACTH 22.21 mg/ml (4.7–41), cortisol 436.6 nmol/l (123–628), FSH 19.6 U/L, LH 24.3 U/L, prolactin 214.1 mU/l (90–540), IGF1 76.67 (54–210). MRI revealed pituitary adenoma 16×20×13 mm with supra- and parasellar extensions. Intraoperatively the tumor occupied all of the sella space, infiltrated the pituitary and was closely attached to the back wall of the sela turcica.

The postsurgical period starting from 2 days was complicated by antidiuresis (fluid intake 2000–2700 ml, diuresis 1000–1200 ml), neurological disturbances (fatigue, vertigo, shaky walk), Postoperative hypothyroidism and hypocortisolism were excluded. The lab tests were only notable for hyponatremia – 126 mmol/l (135–146). The i.v. therapy with normal saline (3% was not available), oral fluid intake restriction, increased oral salt intake, fludrocortsone 0.1 mg a day, did not correct the clinical situation with variable electrolyte values in subsequent 4 days (Na 127–117 mmol/l, K 4.0–3.6 mmol/l, CI 93–80 mmol/l, plasma osmolality 0.274–0.243 Osm/kg with inappropriately high urine osmolality 0.541–0.470 Osm/kg). The patient’s condition improved and Na normalization (139 mmol/l) occurred only after discontinuation of hydrochlorothiazide.

After that fludrocortsone was withheld and no water-electrolyte disturbances were detected at follow-up control. Thereby, this clinical situation was considerate as thiazide-induced antidiuresis.

Conclusions

The case of our patient raises the problem of hard differential diagnosis and treatment of hyponatremia in patients undergoing transsphenoidal surgery.

DOI: 10.1530/endoabs.32.P951

An acromegalic patient with giant tumor

Gulcin Cengiz Ecemis, Elif Kilic Kan, Cigdem Turan Bahadir, Aysegul Atmaca, Hulusi Atmaca & Ramis Colak
Endocrinology Department, Faculty of Medicine, Ondokuz Mayis University, Samsun, Turkey.

Introduction

Acromegaly is a disease caused by excessive secretion of GH. The cause of acromegaly is GH secreting pituitary adenoma in 99% of the cases. It is estimated that 5% of pituitary adenomas become invasive and may grow to gigantic sizes (>4 cm in diameter). Here, we present a 31 years old acromegalic woman with a delayed diagnosis of a giant invasive pituitary adenoma.

Case report

A 31-year-old woman admitted to our hospital for oligomenorrhea and loss of vision. She had a history of infertility for 10 years. She received IVF five times. Her FSH was 0.43 (3.5–12.5) mU/ml, LH was 0.07 (2.4–12.6) mU/ml, prolactin was 27 ng/ml (4.7–23) and IGF1 was 984 ng/ml (116–307 for her age). Her nadir GH level during a 75 g oral glucose tolerance test was 14.8 mg/dl. Pituitary magnetic resonance imaging revealed a 72×47×68 mm macroadenoma with necrotic components which invades suprasellar region and sphenoid sinus and destructs sphenoid bone. Despite a giant macroadenoma her thyrotrtophes and corticotrophes were not affected. She had normal thyroid and adrenal functions. She had transcranial removal of the adenoma and histopathological diagnosis was eosinophilic somatotroph adenoma. Immunohistochemical staining was positive for GH. Postoperatively, she had severe hyponatremia and she was followed in intensive care unit. She died in her second postoperative day with severe electrolyte imbalance.

Conclusions

Delayed diagnosis of acromegaly may lead to growth of a giant macroadenoma which then increases the likelihood of morbidity, postoperative complications and mortality.

DOI: 10.1530/endoabs.32.P952

Hyperprolactinemia in women

Liudmila Kushnir
Belarussian State Medical University, Minsk, Belarus.

The aim of this study was to determine the structure of the primary incidence of hyperprolactinemia among the female population of the city during 2011. 114 medical cards of women with hyperprolactinemia were researched and analyzed. It was determined that the mean age of the case detection was 28.9 years (σ=8.2). The main clinical features were the disturbances of menstrual period (41.2%), infertility (26.3%), galactorrhea (21.9%) and the changes of the body weight (7.9%). Among the disturbances of menstrual period were amenorrhea (40%) and irregular menstruation (60%). The majority (73%) of women with infertility have no any other clinical features. By the end of 2011 the pituitary MRI scan was performed in 81 women with hyperprolactinemia. The results of the pituitary MRI showed that 72% (58) of women with hyperprolactinemia had microadenomas,
6% (5) had probable signs of microadenomas, 22% (18) had no signs of microadenoma. 63% (20) of hyperprolactinemic women with the disturbances of menstrual period had microadenomas, 9% (3) had probable signs of microadenomas, 28% (9) had no signs of microadenoma. 72% (18) of infertile women with hyperprolactinemia had microadenomas, 4% (1) had probable signs of microadenomas, 24% (9) had no signs of microadenoma. 100% (17) hyperprolactinemic women with galactorrhea had microadenomas. The results show that it’s necessary to test a serum prolactin of infertile women. The pituitary MRI in hyperprolactinemic women is recommended to diagnose a microadenoma.

DOI: 10.1530/endoabs.32.P953

P954
Radiotherapy in the management of pituitary functioning adenomas: a single-center experience
Carolina Moreno, Isabel Paiva, Leonor Gomes, Luísa Ruas, Sofia Gouveia, Joana Saraiva, Daniela Guelho, Manuela Carvalheiro & Francisco Carrilho
Department of Endocrinology, Diabetes and Metabolism, University Hospital of Coimbra, Coimbra, Portugal.

Introduction
Radiotherapy is an effective treatment for relapsing or recurrent pituitary functioning adenomas, providing tumor volume control and hormone secretion normalization. However, there are several secondary effects to consider.

Aims:
To assess the efficacy of radiotherapy in the management of patients with acromegaly and Cushing’s disease (CD) treated in our Department, and the prevalence of radiation secondary effects.

Methods
Retrospective analysis of clinical data, hormonal and radiological parameters of all the patients with acromegaly and CD submitted to radiotherapy from 1989 until present time.

Results
Total of 28 patients, 7f (25%) and 21f (75%); 75% with acromegaly and 25% with CD. Fractionated external beam radiotherapy was performed in 78.6%, GammaKnife radiosurgery in 14.3% and fractionated stereotactic conformal radiotherapy in 7.1%.

In the acromegaly group, all the patients had previous pituitary surgery. Thirteen patients (61.9%) had also therapy with somatostatin analogs that were discontinued after radiotherapy in 28.6% of the cases. Remission was achieved in 42.9% of the patients after 109.5 ± 68.9 months. Tumor volume reduction was visible in 61.9% of the cases after 85.2 ± 62.4 months.

In the CD group, six patients (85.7%) were previously submitted to surgery. All of them were under steroid synthesis inhibitors for 48.3 ± 66.6 months, which were stopped after radiotherapy in every patient. Remission was achieved in four patients (57.1%), after 70 ± 61.1 months. There was tumor shrinkage in six cases (85.8%), after 67 ± 61.8 months.

The reported secondary effects were: stroke in one patient, meningoencephalitis in one, epilepsy in two and dementia in one. Of the 11 (39.3%) patients with previous hypopituitarism, 4 (36.4%) worsened the number of deficits. There was de novo hypopituitarism in nine patients (32.1%).

Conclusion
In this sample, radiotherapy was effective in the normalization of hormonal hypersecretion (remission) in 46.4% of the patients, and tumor volume control (decrease of the tumor residue) in 67.9%. The most prevalent secondary effect was hypopituitarism (68.5%).

DOI: 10.1530/endoabs.32.P955

P955
Atypical McCune–Albright syndrome associated with GH secreting pituitary adenoma
Gordana Pemovska, Cvetanka Volkanovska - Ilievkska, Brankica Krstevska & Irfan Ahmeti
University Clinic of Endocrinology, Skopje, Macedonia.

McCune–Albright syndrome (MAS) is characterized by fibrous dysplasia (FD), cutaneous café-au-lait pigmentation and autonomous hyper-secretory endocrinopathies. Association of acromegaly with MAS is very rare. We present a case of a 35-year-old man with MAS, diagnosed with poly-ostotic fibrous dysplasia at the age of 12, no history of premature puberty, with GH secreting cystic macroadenoma 40 × 35 × 45 mm big and clinical picture of acromegaly, hypopituitarism and bilateral hemiopia. FD was diagnosed based on the clinical picture, radiological findings and bone scan.

Base values of the hormones were: GH 16.6 mg/ml with absent supression OGTT, IGF1 > 1100 mg/ml, IGFBP=9800 mg/ml, PRL > 470 mg/ml. Our patient was treated with somatostatin analog, Octreotide 3×0.1 mg for 2 months prior to transphenoidal surgery. Due to residual and activity of acromegaly, the patient was treated with external irradiation and dopamine agonist Bromergon until normal values of GH/IGF1 were achieved. One year after the surgery, FD of cranial bones caused fascial asymmetry, ptosis of the right eyelid, strabismus, sight impairments. After Craniotomia frontofemoralis dex. Decompressio optici dex. were performed, the symptoms disappeared.

The pathohistological findings showed Osteoma (FD) of the scalp in the right occipital region. The patient is on substitution therapy with l-thyroxine, testosterone and bisphosphonate.

As conclusion, primary treatment of large pituitary mass is surgery. Nonurgical treatment, in inoperable patients due to bony involvement of the skull are somatostatin analogs, radiotherapy and dopamine agonists at maximal doses.

Key words: McCune–Albright syndrome, acromegaly.

DOI: 10.1530/endoabs.32.P955

P956
Hyponatremia as a first sign of panhypopituitarism: empty sella
Adriana Dokupilova1, Jana Kollerova2 & Juraj Payer2
1Cardiology Department, Nitra, Slovakia; 2Department of Internal Medicine, Bratislava, Slovakia.

Introduction
Hyponatremia is the most common disorder of electrolytes encountered in clinical practice, occurring in up to 15–30% of both acutely and chronically hospitalized patients. Although most cases are mild and relatively asymptomatic, it is important clinically because: i) acute severe hyponatremia can cause substantial morbidity and mortality, ii) mortality is higher in patients with hyponatremia who have a wide range of underlying diseases and iii) overly rapid correction of chronic hyponatremia can cause severe neurologic deficits and death.

Hyponatremia as the presenting manifestation of empty sella syndrome is rare. The term empty sella makes reference to the herniation of the subarachnoid space within the sella in patients with no history of pituitary tumor, surgery or radiotherapy. Although it is not usually associated with endocrine abnormalities, different degrees of hypopituitarism and mild hyperprolactinemia have been reported. Its clinical presentation resembles that of the syndrome of inappropriate antidiuretic hormone (ADH) secretion, but fluid restriction alone is unable to correct this problem. The cause of ADH secretion in hyponatremia associated with hypopituitarism is related to adrenocortical deficiency. The glucocorticoid deficit is not an osmotic, but a physiological stimulus for ADH secretion. Glucocorticoids have been shown to reverse the impaired water diuresis of this disorder by increasing the renal excretion of solute-free water. Glucocorticoid substitution is the mainstay treatment in this setting, but there are no practical guidelines for optimal glucocorticoid correction. In reviewing the literature, the dosage of hormone substitution has varied. Frequent monitoring of natremia is necessary to prevent neurologic deficits and myelinolysis.

Case report
A 38-year-old patient was admitted to our Department in April/May 2011 due to dyspepsia, nausea and vomiting. Patient had a history of NSA (nimesulide) 14 day before admission, after falling down he complained of the pain in the right thorax. On the date of admission he had following laboratory findings: severe hyponatremia 118.8 (reference range RR 135–145 mmol/l), low serum osmolality 240 (275–295 mOsm/kg), urine osmolality 547 (50–1400 mOsm/kg), uTSH 2.92 (0.3–4.2 µU/ml), serum cortisol level at 0900 h was 616 (500 nmol/l and more), mild anemia Hb 117 (130–180 g/l). He suffered from asthma and had meningitis in 1994. He had no liver and renal disease and never drank alcohol, he denied any history of using diuretics. His weight was 71 kg, his height was 171 cm, pulse rate 58 beats/min, respiratory rate 19/min, blood pressure 110/70 mmHg, temperature 36.7 °C. He was clinically euvoletic. Patient underwent gastroscopy with conclusion: minimal antrum gastritis and dysmotility like dyspepsia. Colonoscopy was without pathologic findings. CT of thorax and abdomen was without traumatic or other pathological changes, as well as CT of brain. After water restriction the serum sodium level normalised and patient was discharged. According to baseline laboratory findings, thyroid and severe adrenocortical deficiency was excluded. The follow up laboratory findings in
P957

Somatotrop adenomas: comparison between men and women in Algerian population

Katta Daffeur, Meriem Haddad, Fatima Saraoui, Lina Akkache, Nadia Kalafate, Djamila Meskine & Farida Chentli
Department of Endocrine and Metabolic Diseases, Bab Oued Hospital, Algiers, Algeria.

Introduction
Pituitary adenomas in general are deemed to be more aggressive in males. Our aim is to analyze somatotrop adenomas (SA) characteristics and neurological complications. In the second time we will compare male and female cases.

Subjects and methods
In this retrospective and prospective study, 112 pure and mixed SA diagnosed between 1980 and 2012 were analyzed. All had hormonal assessment (GH before and after OGTT ± IGF1, PRL, cortisol, ACTH, testosterone/E2, FSH, LH, TSH, FT4, FT3), ophthalmological examination and cerebral CT scan, or MRI or both.

Results
Sex ratio = 1, mean age 39.11 years (14-60). Paediatric forms = 8.03%. Mean tumour volume = 117.1 mm³. Giant forms (height ≥ 40 mm) = 10%. Mean GH = 62.3 ng/ml. IGF1 was increased in all tested cases. cavernous system invasion was observed in 42.15%. Gonadotroph deficit = 44.8%, corticotrop = 22.22% and thyreotrop = 21.99%. Global pituitary insufficiency = 4.58%. Posterior pituitary deficit = 0%. Optic atrophy = 2.9%. We did not observe any severe neurological complications such as hydrocephalus, convulsions, frontal syndrome, meningitis, memory troubles and unconsciousness, but we had some apoplexy.

Sexual comparison showed men were diagnosed later (39.89 years vs 30.33, P = 0.01). We did not find any difference in tumour volume and GH rate before and after OGTT, but women had more invasive tumours (P = 0.03). Thyreotrop and gonadotroph deficits were more frequent in women (respectively P = 0.016, 0.000075).

Conclusion
In this study where the sex-ratio is equal to one, female cases appeared more aggressive although male cases were diagnosed later. To explain this difference the role of estrogens should be discussed.

DOI: 10.1530/endoabs.32.P957

P959

Assessment of bone mineral density in patients with Sheehan’s syndrome

Fatih Kilici, Fetah Acibucu & Hatic Sebilla Dokmetas
Department of Endocrinology and Metabolism, Cumhuriyet University, Sivas, Turkey.

Introduction
Although the cause and effect relationship between the hypophysial deficiency and osteoporosis is known well, the number of studies concerning bone mineral density (BMD) in patients with Sheehan’s syndrome (SS) are scarce. We aimed to investigate the relationship between BMD and deficient hormones in patients with newly-diagnosed Sheehan’s syndrome.

Material and methods
Thirty-four patients with SS and age-gender-weight matched 22 controls were included in the study. Demographic data, biochemical hormonal values and BMD of the patients were recorded.

Results
We found osteoporosis in 61.8%, osteopenia in 32.3%, and normal dual energy X-ray absorptiometry (DEXA) findings in 5.9% patients. In the control group 68.2% of individuals were osteopenic and 31.8% of them were normal. The number of osteoporotic patients was found to be higher and BMD values lower in the patient group compared with the control group. There was no relation of DEXA measurements with the period between the last delivery and the initial diagnosis and the estradiol levels. While there was no relation between IGF1 and T and Z scores of femur head but the relation between the of IGF1 and L1-L4 T scores was statistically significant (P = 0.010). There was a significant relation between the IGF1 and L1-L4 Z scores (P = 0.001).

Conclusion
SS patients had decreased BMD values compared with age-gender-weight adjusted control group. In conclusion SS patients should also be assessed in terms of osteoporosis at the time of diagnosis and then proper treatment should be initiated afterwards.

Key words
Sheehan’s syndrome, BMD, hypophyseal deficiency.

DOI: 10.1530/endoabs.32.P959

P960

Giant invasive macroprolactinoma 2: case report

Fella Hasbellaoui, Samia Amokrane, Samia Achtir, Ibtissem Bouraoui & Mourad Sennouini
Endocrinology and Nuclear Medicine Department, Centre Pierre et Marie Curie, Algiers, Algeria.

Introduction
Prolactinoma are the most frequent pituitary adenoma, considered benign tumor and well respond to medical treatment, but sometimes, in men prolactinoma may be invasive and aggressive occurring neurological signs.

Endocrine Abstracts (2013) Vol 32
Case 1

Male 53 years old, went to ophthalmology consulting for progressive vision problems associated with headaches from more than a year but denied. On examination visual field showed poor vision in left eye and temporal defect on right one.

CT scan and MRI showed a large invasive mass in the skull base with destruction of sella turcica and compression of brain parenchyma with hydrocephaly (80 mm).

He was sent to neurosurgery, the first hypophysis chordoma or meningioma. He had hypogonadism and hypothyroid clinical signs. The hormonal evaluation revealed an hyperprolactinemia 22 000 ng/ml. treatment with dopamine agonist was begun with anti epileptic drugs.

The evolution prolactin levels stabilized, MRI showed partial reduction of the volume at 1 year (30%) and more than 80% at 4 years. thickness problems improve but did not recover. Hypothyroidism is treated.

Case 2

Male 36 years old, went consulting to neurology for progressive headaches, dizziness, time and space disorientation, double vision and recently blindness in right eye. MRI revealed a large invasive lesion extending to the supra sella cistern, the optic chiasma and the brain parenchyma in left temporal lobe 75/60 mm.

He was evaluated in endocrinology, tests revealed an hyperprolactinemia 12 000 ng/ml. hypocortisolism and hypogonadism.

He was don dopamine agonist at 2 months he presented an apoplexy with ophthalmoplegy and convulsion with rapid recovery.

At 1 year partial tumor reduction (50%) and prolactin level stabilized. At 3 year we obtained an empty sella turcica, an improvement of visual problems.

Conclusion The importance of hormonal evaluation in cerebral tumors. The responsiveness of these tumor to dopamine agonists confirm the medical option in prolactinoma even when invasive.

P962

Can apelin level used as a marker of active and inactive acromegaly?

Senay Topsakal1, Fulya Akin1, Guzin Yaylali1, Sebahat Turgut1, Duygu Herek2, Enrah Yerlikaya1 & Ceylan Ayada1

1Department of Endocrinology, Pamukkale University, Denizli, Turkey; 2Department of Physiology, Pamukkale University, Denizli, Turkey.

Introduction

Acromegaly is a rare disease that is most often caused by a GH secreting pituitary tumor. Apelin, a newly discovered peptide known as an endogenous ligand for its receptor (API) is a cardiac positive inotropic factor that has also hypotensive effects. The apelin and its receptor functions have not entirely been understood yet. The physiological importance of apelin, in acromegaly remains obscure.

The aim of this study was to investigate the differences of apelin levels in active and inactive acromegalic patients.

Methods

In this study 37 acromegalic patients (20 inactive and 17 active acromegaly) and 30 controls were included to the study. Patients with GH ≤ 1 ng/l and IGF1 were in normal levels according to ages and sex were classified as inactive; and patients with GH >1 ng/l and higher IGF1 levels were classified as active acromegaly.

Apelin serum level were measured by ELISA method.

Results

Although slight decrease were observed inactive and active acromegalic patients, we couldn’t find any statistically significant differences in apelin levels in inactive and active acromegalic patients, but we observed more than 11-fold higher apelin levels in active acromegalic patients compared to controls and results were statistically significant.

Conclusion

We found high levels of apelin in active acromegalic patients. Apelin levels can not to be used the marker of active acromegaly.

DOI: 10.1530/endoabs.32.P962

P961

Pituitary hyperplasia secondary to primary hypothyroidism in a child with mosaic trisomy 21

Faiza Belhimer & Farida Chentli

Department of Endocrinology and Metabolism, Bab El Oued Hospital, Algiers, Algeria.

Introduction

Pituitary hyperplasia (PH) is relatively a rare condition in children. As in adults, it can be secondary to a long-standing primary hypothyroidism and can sometimes be mistaken with a pituitary macro-adenoma as in the following observation:

Case report

Herein, authors describe a girl aged 10 years old sent by her neurosurgeon for progressive headaches, dizziness, time and space disorientation, double vision and recently blindness in right eye.

Clinical examination revealed a discrete growth retardation (~1.5 SD/TS).

The rest of clinical examination did not find anything abnormal except a particular shape of her eyes that look like Mongol’s. The karyotype confirmed our impression as it showed a mosaic form (15%). Thyroid assessment showed increased TSH (8 IU/ml). Thyroid ultrasound demonstrated an hypo-echoic gland. Thyroperoxidase antibodies were increased arguing for an autoimmune origin which is common in patients with Down syndrome. Under 100 μg levothyroxine TSH and TH were normalized.

Conclusion

The association of primary thyroid deficit with a pituitary lesion argued for a secondary thyrotrophic pituitary adenoma which is relatively rare in children. But, this diagnosis was confirmed in retrospect by MRI that showed a normalization of pituitary size under 100 μg levothyroxine. Pituitary hyperplasia due to puberty or hypothyroidism should be known by neurosurgeons who are not used to this conditions.

DOI: 10.1530/endoabs.32.P961

P963

Pasireotide in treatment of Cushing’s disease: our first experience

Peter Vanuga, Peter Kentos, Dušan Pavai Jr & Mikuláš Puru

Department of Endocrinology, National Institute of Endocrinology and Diabetology, Lubochna, Slovakia.

Background

As corticotroph adenomas express somatostatin (SST) receptors (SSTRs), pasireotide – a pluripotent somatostatin analogue, acting on four of five SSTRs has a potential role in treatment of CD among various medical agents.

Case report

We report a 39-year-old female with recurrence of Cushing’s disease (CD) 9 years after the initial successful pituitary surgery. Medical treatment with ketoconazole has to be stopped due to headache and myalgia, therefore pasireotide at dose 0.6 mg s.c. twice daily was started. Increased serum cortisol (FP) levels with loss of circadian rhythm (779–398–435–627–607 nmol/l at 0800–1600–2000–2400–0800 h respectively), with increased basal urinary free cortisol (UFC) (1767–1848 nmol/day), non-suppressible in 2 mg (FP 231 nmol/l, UFC 358 nmol/l) and non-suppressed ACTH levels (45.0 pg/ml) decreased even 4 days after starting the treatment – FP levels 281–156–206–140–300 nmol/l (taken at same times), ACTH 32.7 pg/ml. After 2 months, FP were 517–357–181–360–339 nmol/l, UFC 987,799 nmol/l, ACTH (39.7 pg/ml) was not changed. Parameters of glucose metabolism were changed non-significantly – HbA1c (IFCC) 3.91–4.48% (normal value 2.0–4.2%), mean daily glucose levels 6.47–7.27 mmol/l (normal values 3.50–5.90 mmol/l).

Discussion:

After 2 months of the treatment, we stated good effect of treatment, with decrease of ACTH (12%), FP (basal 34%, midnight 43%, average 36%), and UFC levels (49%). Patient tolerated treatment with pasireotide well, but suffered from mild persistent diarrhoea as an adverse effect of the treatment. Diarrhoea is potential side effect of SSTR-analogs and was also recorded as the most frequent side effect of pasireotide in pilot study by Colao et al. (N Engl J Med 2012).

DOI: 10.1530/endoabs.32.P963
P964
Corticotroph adenoma and fertility
Lila Brakni
Department of Endocrinology, Algiers, Algeria.

Introduction
The occurrence of a pregnancy in a woman with a corticotroph adenoma is rare, <25 observations have been reported.
Maternal complications are especially hypertension (60–75%) gestational diabetes (25%) and preeclampsia in 10%.
Fetal complications are spontaneous miscarriage, preterm birth and intrauterine growth retardation.

Observation
We report a case of a 30 years old female followed for primary subfertility. The diagnosis of Cushings disease is withheld to: obesity, amenorrhea, hypertension and osteoporosis
- Cortisol at midnight = 712 nmol/l
- Cortisol at 0800 h = 809.4 nmol/l ACTH = 9 pg/ml
- Low braking: negative
- Strong braking: positive
- Pituitary MRI: microadenoma 6.4 mm.

Under anti-cortisol arrested 2 weeks later for liver toxicity. The resection of microadenoma was delayed because he was 6 weeks pregnant. Noting a gestational diabetes than the 24 th week. Delivery term. After 2 years of remission (post resection) a 2 nd spontaneous pregnancy with abortion at 12 weeks.

Conclusion
The impact of secretions ACTH of pregnancy requires a multidisciplinary support.
DOI: 10.1530/endoabs.32.P964

P965
Central hypothyroidism and adjusted thyroxine dose study (CHATS): impact of increasing free thyroxine levels in patients with hypopituitarism
Anna-Elisabeth H Minder1, Andreas Jostel2, Claire E Higham 1, W David J Ryder3, Peter J Trainer 1 & Stephen M Shalet 1
1Department of Endocrinology, The Christie NHS Foundation Trust, Manchester, UK; 2Department of Medical Statistics, The Christie NHS Foundation Trust, Manchester, UK.

Introduction
Patients with pituitary deficiencies suffer from impaired quality of life regardless of substitution therapy with hydrocortisone, thyroxine (T4), sex hormones or GH. Central hypothyroidism (CH) is difficult to diagnose and treat because symptoms are non-specific and TSH-levels cannot be used for assessment. There is no consensus for the T4-goal of thyroxine-replacement in patients with CH.

Aim
To determine the impact of increased T4 on quality of life in patients with hypopituitarism.

Methods
Randomized, double-blind, placebo-controlled trial of additional T4-supplementation. 40 patients (age 20–70 years) with hypopituitarism and T4-levels in the lowest third of normal reference range were included. Patients received placebo or T4-titration aiming for T4 levels in the upper third of reference range, irrespective of TSH values. Total study duration 42 weeks (24 weeks dose adjustment, 18 weeks stable dose). Quality of life assessments (QoL) using four questionnaires (SF-36v2, PGWBS, EQ-5D, AGHDA) at baseline and end of study. Statistics were performed using an analysis of covariance.

Results
The increase in T4-values in the treatment group did not translate into significant changes in vitality score as assessed by SF-36v2 (estimated treatment effect 4.65 (95% CI – 7.86, 17.15) or general health score (estimated treatment effect is 1.57 (–8.19, 11.33)), nor in any of the other questionnaires (PGWBS = 1.11 (–8.80, 6.58); AGHDA 0.88 (–2.27, 4.53); EQ5D-VAS – 4.40 (–13.45, 4.65)).

Conclusion
The increase of T4 to the upper third of normal range did not significantly change the vitality score, general health or quality of life in hypopituitary patients and therefore does not provide support for the commonly used strategy of thyroxine-supplementation to the upper limit of normal. With 40 patients, however, the study may be underpowered to detect small effects. Other explanations for lack of effect include an inappropriately high or low T4 goal and further research is required.
DOI: 10.1530/endoabs.32.P965

P966
A retrospective-prospective study of the effect of octreotide LAR in acromegalic patients
Gordana Pemovska, Ance Volkanovska, Biljana Jovanoska & Slavija Shubeska-Stratrova
University Clinic of Endocrinology, Skopje, Macedonia.

Objective
Surgery is considered first-line treatment for pituitary GH secreting macro-adenoma. Since surgical removal of the pituitary tumor is subtotal, medical treatment has become the mainstay of acromegaly. The aim of our study was to assess the effect of octreotide LAR (OCT-LAR) therapy in patients with acromegaly.

Patients and methods
Ten acromegalic patients were treated with OCT-LAR 20 mg/28 days. The effect was evaluated after 12 months of treatment. Eight patients received OCT-LAR as adjunctive therapy after surgical debulking, and two as primary treatment. Tumor size was assessed with pituitary magnetic resonance imaging (MRI) before the treatment and after 12 months. Biochemical evaluation was performed at baseline, 6 and 12 months after beginning OCT-LAR. Normalization of IGF1 was considered as biochemical remission of active acromegaly.

Results
Among the evaluated patients five were males and five females, mean age 40.2 ± 8.04 years (age range: 30–50 years). After 12 months of treatment biochemical remission (normalization of IGF1 levels) of acromegaly was achieved in nine patients. Values of IGF1 after 6 and 12 months showed a mean decrease of 55.69 and 71.53% respectively. Average tumor size before treatment and after 12 months was 17.7 and 10.42 mm respectively with an average decrease of 48.18% in size. Also, GH levels were evaluated and showed a mean decrease of 74.57% after 12 months. Along the treatment significant improvements in headache, arthralgia, sweating and soft tissue swelling was attained.

Conclusions
Treatment with OCT-LAR can be considered as effective therapy in achieving biochemical remission and tumor shrinkage in active acromegaly. Given its efficacy and safety it is a treatment of option as primary therapy in patients who are at risk or refuse operative treatment.

Keywords
Acromegaly, octreotide LAR, GH, IGF.
DOI: 10.1530/endoabs.32.P966

P967
Craneopahrygioma: a false enemy
Jaime Lorenzo, Ruth Boente, Eloisa Santos & Manuel Sas
Hospital povisa, Vigo, Spain.

Background
Craneopharygioma is a rare solid or mixed tumor, that arise from remnants of Rathke’s pouch. Usually they are in the suprasellar region and very few of them arise from the sella. Bimodal (5–14 years old and 50–75) and slow growth are typical characteristics as well.

Clinical case
A 20 years old boy was refered to endocrine clinic by hypothyroidism, hypopituitarism, and sexual dysfunction. Central hypothyroidism, hypogonadotropic hypogonadism and secondary adrenal insufficiency due to sellar mass was diagnosed. Sellar and suprasellar mixed mass with solid and cystic changes were found and due to its stability for 5 years and because of the clinical presentation was interpreted as a macroadenoma. Sustituitive hormone treatment is prescribed and regular clinical and radiologic follow up is made. For 5 years the mass experimented no changes but in the next evaluation mass enlargement with significant suprasellar extension was seen. Periical cranectomy are made and a craneopharygioma is diagnosed. Treatment is completed with stereotactic radiotherapy and the patient has a good response so far.

Discussion
Usually calcification in the suprasellar region is seen up to 80% and cyst are present very often (up to 75%). If calcification is not seen, suspicion is more
Steroid metabolism and action

P968

Androgenic and estrogenic regulation of skeletal muscle mass and atrophy signaling in male mice

Hélène De Naeyer1, Inge Everaert1, Annelies De Spaay2, Jean-Marc Kaufman1, Youyi Taes1 & Wim Derave2

1Department of Movement and Sports Sciences, Ghent University, Ghent, Belgium; 2Department of Endocrinology, Ghent University Hospital, Ghent, Belgium.

Background

Hypogonadism in men is associated with low muscle mass and force. Although, androgen replacement is an effective therapy, it can have undesirable side effects. Identifying the androgen regulated molecular mechanisms that increase muscle mass and function could lead to the identification of novel muscle-specific therapeutic targets to improve the clinical outcomes of muscle wasting diseases. In this study, we examined in mice the effects of orchidectomy (after 1, 7 and 30 days), either with or without testosterone or estradiol (E2) administration, on the muscle-specific ubiquitin protein ligases Atrogin-1, MuRF1 and myostatin gene and protein expression.

Methods

Measurements were made in slow-twitch soleus (SOL), fast-twitch extensor digitorum longus (EDL) and androgen-sensitive levator ani/bulbocavernous (LA/BC) muscle of male C57BL/6 mice.

Results

Thirty days of orchidectomy was associated with a significant decrease in muscle strength and muscle mass in SOL (13.8%), EDL (12.9%) and LA/BC (63%). These effects were prevented by testosterone treatment. In the LA/BC muscle, Atrogin-1 and MuRF1 mRNA were increased throughout the 30 days of androgen deprivation, which was fully reversed by testosterone administration and partially reversed by E2 administration. In SOL and EDL, a less pronounced upregulation of both genes was only detectable at the early stages of orchidectomy. Myostatin mRNA levels were upregulated in EDL. However, these changes were not paralleled by changes in the protein levels of Atrogin-1, MuRF1 and myostatin at any time point following orchidectomy. Our data indicate important differences in orchidectomy-induced skeletal muscle atrophy between LA/BC and the locomotor muscles.

Conclusion

These findings also question role of Atrogin-1, MuRF1 and myostatin in this model of muscle atrophy and suggest that other proteolytic targets are responsible for the loss in SOL and EDL muscles mass after androgen deprivation.

DOI: 10.1530/endoabs.32.P968

P969

Cross-sex hormone therapy related adverse events: data from a large gender identity unit

Katrien Wierckx1, Edward Anseeuw2, Lieselot Geerts1, Els Elaut1,2, Gunter Heylen2, Joz Motmans1,2, Griet Decuyper1 & Guy T Spoel1,2

1Department of Endocrinology, Ghent University Hospital, Ghent, Belgium; 2Department of Sexology and Gender Problems, Ghent University Hospital, Ghent, Belgium.

Introduction

Hormonal therapy is part of an established treatment of gender identity disorder, however outcome data regarding mortality and morbidity are scant.

Methods

A specialist center cross-sectional study in 193 transsexual women and 128 transsexual men (mean age 42.5 years) assessing physical health and incidence of possible treatment related adverse events compared to an age-matched female and male control group recruited from a population study in Flanders (1–3 matching). Participants on average used 7.4 years of cross-sex hormone therapy (range: 3 months–49 years) and were 6.6 years since sex reassignment surgery (SRS).

Results

Ten transsexual persons (one transsexual man and nine transsexual women) died during follow-up. Causes of death were suicide, cardiovascular disease (n=2), cancer (n=2) and suicide (n=6). Three percentage of transsexual women (n=10) experienced venous thrombosis and/or pulmonary embolism during hormonal therapy. Half of them occurred during the first treatment year (n=5), another three at time of SRS. Transsexual women experienced more myocardial infarction (MI) compared to control women (P=0.001) but not to control men. Prevalence of cerebrovascular disease (CVD) was higher in transsexual women compared to control men and women (P=0.05 and P=0.02; respectively). Transsexual men had similar morbidity rates of MI and CVD compared to control population.

Prevalence of type 2 diabetes was higher in both transsexual men and women compared to control women. However, all but one diagnosis in transsexual women were found before start of hormonal therapy suggesting overdiagnosis. We observed an equal prevalence of cancers and HIV infection in transsexual persons compared to control population.

Conclusion

Data of the current study indicate a higher mortality rate in transsexual women and more venous thrombosis, MI and CVD. Transsexual men had similar morbidity rates compared to the general population, apart from a higher incidence of type 2 diabetes.

DOI: 10.1530/endoabs.32.P969

P970

Screening for Cushing’s syndrome in obese patients

María Rosa Alhambra Expósito, Carmen Tenorio Jiménez, Inmaculada Prior Sánchez, María José Molina Puerta, Paloma Moreno Moreno, Concepción Muñoz Jiménez, María Angeles Gámez Moreno & Pedro Benito López

Hospital Reina Sofía, Córdoba, Andalucía, Spain.

Background

Cushing’s syndrome (CS) is considered to be more frequent among patients with metabolic syndrome. Previous studies have suggested to perform a routine screening for CS in obese patients; however, more recent reports only recommend a case-finding approach in patients with uncontrolled diabetes and hypertension, despite appropriate treatment.

Objective

The aim of this study was to evaluate the prevalence of unsuspected CS in morbidly obese patients in an outpatient’s clinic.

Design

Retrospective case-note study.

Patients and methods

We reviewed the medical records of morbidly obese patients referred to our clinic prior to bariatric surgery between January 2001 and December 2011. All patients had a complete medical history including physical examination, and 387 (300 females; mean age 46.5±11.2 years; mean BMI 52.8±27.1 kg/m²) underwent screening for CS as part of our pre-surgical protocol. As screening for autonomous cortisol secretion, we performed an overnight 1 mg dexamethasone suppression test (DST). Serum cortisol <1.8 μg/dl was the cut-off point for normal suppression.

Results

In the retrospective analysis, prediabetes and diabetes mellitus were observed in 10.20 and 26.40% respectively. In 20 of 387 patients, screening was considered to be abnormal. Seven of these 20 patients had subsequent normal 24 h urinary free cortisol (UFC) levels (150 μg/24 h). In 13 of 20 patients, we repeated an overnight 1 mg DST, on suspicion of failing to take the dexamethasone correctly. Three patients failed to suppress their cortisol levels, two of them were on carbamazepine, which was considered to be a false positive result. The other patient with abnormal UFC levels was diagnosed with CS (0.26%), whose cause was a pituitary microadenoma.

Conclusion

A low proportion of patients with morbid obesity were found to have CS. Our findings suggest that morbidly obese patients should not be routinely screened for CS.

DOI: 10.1530/endoabs.32.P970
Using real-time PCR, we found that RDH12 is highly expressed in the skin of Macaca fascicularis (mf). It has been known that RDH12 is a retinol dehydrogenase that catalyzes the reduction of retinol into retinal and play an important role in the visual cycle. Indeed, its deficiency is the cause of Leber’s congenital amaurosis 3, a genetic disorder characterized by retinal dystrophy, affecting both rods and cones. Previously, we have shown that many of the members of the retinol dehydrogenase family, such as RDH1, 5, 11 and 16 could also metabolize 5a-reduced steroids, including DHT, the most potent natural. In order to determine the possible role of RDH12 in a non-visual cycle and especially in the intracrine metabolism of DHT in the skin, we perform real-time PCR to quantify its expression levels and in situ hybridization to localize its expression in the skin. To determine its activity, we construct expression vectors that express the coding region of human, mf and mouse RDH12 under the control of CMV promoter (pCMV-h,m,mRDH12), and stably transfect the resulting vectors into HEK-293 cells.

Following the transfection, cells are stably expressed human, mouse and mf RDH12 in culture without addition of co-factor, we show that the enzyme catalyzes effectively the transformation of DHT into 3β-diol and 5α-androstane-3β,17β-dione (5α-dione) into 5α-androstane-3β,17β-dione (5α-dione) into 5α-androstane-3β,17β-dione (5α-dione).

Introduction

Critical illness, and sepsis in particular, drives adipose tissue lipolysis up (with triglycerides (TG) being split to free fatty acids (FFA) and glycerol (GLYC)) to meet increased energy demands. Few studies have addressed lipolysis with tissue microdialysis (MD).

Aim

To assess indexes of lipolysis in septic patients with and without shock.

Subjects and methods

The study included 110 men and 73 women (mean age ± s.d.: 62 ± 17 years), 66 with SIRS/severe sepsis (SsSe) and 117 with septic shock (SSho). All the subjects had a tissue MD catheter placed in femoral adipose tissue upon admission to the ICU. Plasma cholesterol, HDL, LDL, FFA, TG and MD GLYC were measured on days 1 and 6 in the ICU. Analysis was done with repeated measures ANOVA and Pearson’s correlation.

Results

Seventy-four patients died. Patients with SSho had lower LDL and higher MD GLYC levels compared to SIRS/SsSe on days 1 and 6. Significant positive correlations were found between FFA and MD GLYC in patients with SSho on day 1 and in patients with SIRS/SsSe on day 6.

Discussion

Lipolysis was apparently acutely more intense in patients with SSho on day 1 and subsequently subsided whereas it became more pronounced in patients with SIRS/SsSe on day 6, verging on chronic critical illness. This dimorphism may provide clues for diversification of nutritional support (carbohydrates vs lipids) in critically ill patients: further studies are warranted.

DOI: 10.1530/endoabs.32.P972

P973

UGT2B17 genotype and pharmacokinetic profile of testosterone during substitution therapy in men with hypogonadism

Anne Kirstine Bang, Niels Jørgensen, Ewa Rajpert-De Meyts & Anders Juul

Department of Growth and Reproduction, Rigshospitalet, Copenhagen, 2100 & Denmark.

Introduction

The UGT2B17 gene encodes a glucuronidase which is important for the urinary excretion of testosterone. Recent studies have shown that a common deletion polymorphism in UGT2B17 is strongly associated with significantly lower levels of excreted urinary testosterone in men. The objective of this study was to investigate the association of the UGT2B17 gene polymorphism and the dosages of testosterone substitution in male patients with Frank hypogonadism.

Material and methods

Two hundred and twenty-eight men treated with Testosterone undecanoate (TU) (Nebido) were retrospectively included. All men were given 1000 mg TU per injection at 0, 6 and 18 weeks. Blood samples were drawn at 0, 2, 6, 12 and 18 weeks after baseline. Sexual hormones were analysed by standard assays, and UGT2B17 genotype was determined by quantitative PCR on isolated DNA from peripheral blood.

Results

Of 13.6% had a homozygote deletions (del/del), 45.0% were heterozygote (del/ins) and 41.2% were homozygote for the wildtype (ins/ins). Before the 3rd injection (18 weeks), nadir serum testosterone levels did not differ between the three groups in total (P = 0.065): median 13.2, 12.7 and 14.0 nmol/l in del/del, del/ins and ins/ins groups, respectively. Estradiol levels tended to be higher in the del/del group (66.5 pmol/l) than in the two other groups (ins/del: 54 pmol/l and ins/ins: 52 pmol/l), although differences did not reach statistical significance. LH, SHBG, the free androgen index (FAI), total cholesterol or haemoglobin did not differ between groups.

At follow-up 2–3 years after initiation of treatment all patients had individual treatment regimes, but no association to genotype was detected.

Conclusion

Nadir serum testosterone levels were not significantly influenced by UGT2B17 genotype in hypogonadal men given standard treatment with TU. Thus, there is no need to consider this genotype as a marker of dosage or interval when initiating testosterone treatment.

DOI: 10.1530/endoabs.32.P973

P974

Effects of food components and the ratio of epistestosterone to testosterone on steroid glucuronidation

Carl Jenkinson, James Barker, Andrea Petroczi & Declan Naughton

Kingston University, Kingston Upon Thames, UK.

The ratio of the glucuronidated epistestosterone (E) and testosterone (T), used in doping tests, is currently under question. The key enzyme involved in E metabolism is UGT2B7 in contrast to T which is mainly metabolised by UGT2B17. Previous results demonstrated that at very high concentrations E acts as a competitive inhibitor to UGT2B17. Similarly, the literature reports competitive inhibition of UGTs by NSAIDS and phenolics that are not substrates of UGT2B17. The aim of this study was to investigate if either T or E glucuronidation is affected by food components (red wine and tea) or by varying ratios of the epimer.

Glucuronidation of T and E was assessed using a novel assay with UGT2B17. The aim of this study was to investigate if either T or E glucuronidation is affected by food components (red wine and tea) or by varying ratios of the epimer.

Glucuronidation of T and E was assessed using a novel assay with UGT2B17.

supersomes and microsomes pooled separately from males and females. HPLC-UV and LC-MS/MS methods were used to monitor E and T glucuronidation at mg/ml and ng/ml levels. Red wine and tea samples were subjected to HPLC analyses to determine their principal active components (catechins and flavonols) which were assessed for inhibitory activity against UGT2B17 and UGT2B7. The effects of T on T glucuronidation were monitored over the concentration range of 0–200 ng/ml E.

The results show that in supersomes the tea samples and red wine along with their component catechins and flavonols exhibit considerable competitive inhibitory activity against UGT2B17 (e.g. IC50 of 64 µM for epigallocatechin gallate). For both microsome and supersome based studies, at 50 ng/ml T, an increase in E resulted in an inhibition of T glucuronidation by up 30% (at T:E 0.5). The use of supersomes also showed variation of testosterone metabolism between males and females as well as varying inhibition levels of T glucuronidation by E. These results highlight the effect of common foods, their components and
P975
Impact of smoking on neuroactive steroids
Hana Hruskovcová1, Michaela Dusková1, Martin Hill1, Karel Vondra1, Eva Králiková2, Luboslav Starka3
1Institute of Endocrinology, Prague, Czech Republic; 2Institute Centre for Tobacco, Dependent of the 3rd Medical Department, the Department of Endocrinology and Metabolism, First Faculty of Medicine and General University Hospital, Prague, Czech Republic.

Introduction
The dependence on tobacco, diagnosis F 17, is an independent condition in the International classification of diseases and presents one of the most widespread addictions. Chronic smoking can cause impairment of fertility in both sexes. However, only a small number of studies were dedicated to the influence of smoking on levels of steroid hormones and their neuroactive metabolites. Neuroactive steroids modulate the effects of tobacco on central nervous system, and also the severity of tobacco dependence. In our study we compared the levels of neuroactive steroids in men smokers and non-smokers and we looked for a possible predictive marker of success in smoking cessation.

Methods
We examined 76 men before initiating the smoking cessation, after 6 weeks and after 1 year of abstinence. According to the success we divided our samples to three groups, 26 men were successful in smoking cessation, 16 men stopped smoking only for 6 weeks and 34 men did not stop smoking at all. We collected samples from a control group of 20 male non-smokers. We measured basic anthropometric data, levels of steroid hormones and their neuroactive metabolites by GC-MS. The local Ethics Committee approved the study and all patients have signed an informed consent form before taking part in the study.

Results
Comparing smokers and non-smokers, we have found lower levels of testosterone, as well as higher levels of FSH, in smokers. Lower levels of testosterone and some neuroactive metabolites of androgens were associated with failure in smoking cessation.

Conclusion
The levels of testosterone and neuroactive metabolites in men successful in smoking cessation were the closest to the levels in the control group. The greater disorder of steroidogenesis, the less probable the success. Funding
The study was supported by grants No. NT 12340-5 and NT 13890-4 IGA MZCR.

DOI: 10.1530/endoabs.32.P975

P976
Changes of steroidogenesis subject to weight growth
Hana Pospíšilová, Michaela Dusková, Martin Hill & Luboslav Horák
Institute of Endocrinology, Prague, Czech Republic.

Introduction
Obesity epidemic has a considerable effect on the health of the population. Obesity is connected with infertility and hypogonadism. It is known that obese men have a low testosterone and higher estradiol level. The assumed mechanism would be increased testosterone aromatization in adipose tissue and a lower SHBG level, which means a decrease of overall testosterone. The aim of this study was to describe the changes of steroidogenesis with obese men.

Methods
We examined a set of 195 men and determined their testosterone (T), dihydrotestosterone (DHT), SHBG, androstendion (A2), DHEA, DHEAS, 17-hydroxyprogesterone (Prod17), 17-hydroxyprogrenolone (Preg17), the Preg17/Prod17, A2/DHEA, DHEA/Preg17, A2/Preg17, DHEA/DHEAS, T/A2 and DHT/T ratios were analysed. The set of men was divided into two groups in accordance with the BMI level.

Results
With BMI over 30 men a higher activity of 3β-hydroxysteroid dehydrogenase and lower activity of sulfatase have been proved. The preferred way of steroid production with obese men is thus 4-way. With men the 4-way is typical, on the contrary the 4-way is typical with women.

Conclusion
We have proved a steroidogenesis shift with obese men that accounts for the T and E2 level change typical with obese men.

Acknowledgement
Supported by IGA MZCR 12340-5, 13890, GAUK 367511 grant.

DOI: 10.1530/endoabs.32.P976

P977
Determinants of between-subject variation in thyroid hormone status in healthy young men
Greet Roet1, Youri Taes1, Kaatje Toye1, Alain Verstraete2, Jean-Marc Kaufman1
1Department of Endocrinology, Ghent University Hospital, Ghent, Belgium; 2Laboratory of clinical Biology–Toxicology, Ghent University Hospital, Ghent, Belgium.

Background
Interindividual variation in thyroid hormone concentrations is greater than intraindividual variation, suggesting that individuals have different set-points for pituitary–thyroid axis function. Variation in thyroid hormone levels within the normal range has clinical effects and is associated with a number of clinical parameters such as bone mass, BMI, metabolic parameters, and heart rate. The aim of this study was therefore to gain a better insight into the determinants of this between-subject variation in thyroid hormone levels in healthy young men.

Methods
Healthy male siblings (n = 941, 25–45 years) were recruited in a cross-sectional, population-based study; a history or treatment of thyroid disease and thyroid autoimmunity were exclusion criteria. In these subjects, a complete assessment of thyroid hormone status was performed (TSH, FT(t), FT(t), TPO and TG Ab, reverse T3 (rT3), TBG and urinary iodine levels). Genotyping was performed by TaqMan SNP Genotyping assays and by KBiosciences.

Results
Total and free T4, rT3, and TBG had heritability estimates between 80 and 90%. Calculated estimates for (FT) were considerably lower (60%), while TSH had the lowest estimate (49%). Significant associations were observed between SNPs in the thyroid pathway (rs4704397 in PDE8B, rs10149689 and rs12050077 in TSHR, rs11206244 and rs2235554 in DIO1 and rs13063628 in THRB) and TSH, FT(t) ratio FT(t)/FT(t) and rT3. Nevertheless, these SNPs only explain a limited part of the between-subject variability in thyroid hormones. As to age and lifestyle related factors, FT(t) was negatively related to age and positively to smoking and BMI (all P < 0.0001) but not to urinary iodine concentrations. Smoking was negatively related to TSH (P = 0.003) and positively to FT(t) (P = 0.0009).

Conclusion
Both genetic and lifestyle-related factors play a role in determining between-subject variation in thyroid hormones in euthyroid young men, although genetic factors are most important.

DOI: 10.1530/endoabs.32.P977

P978
Efficacy of treatment of cardiac complications in patients with Graves’ disease
Elena Leynova & Buydina Tatyana
1Railway Clinic, Yaroslavl, Russia; 2Medical Academy, Yaroslavl, Russia.

Purpose
To assess the dynamics of cardiac complications, the efficacy of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in patients with thyrotoxicosis

Materials and methods
Prospective 4 years study implicated 340 patients with thyrotoxicosis divided into three age groups: I, 80 patients below 40; II, 132 patients of 40–60; and III, 128 patients above 60. By the beginning of the study atrial fibrillation (AF) was diagnosed in 36% of patients of II group, in 41% – of III group; diastolic
**P979**

**Pilot study of nocturnal TSH surge in idiopathic short stature**

Fadila Gadalla, Maged Setouhi, Salwa Sedik, Khaled Makboul, Rania EL Sayed & Caroline Guirgis

Ain shams university, Cairo, Egypt.

**Background**

TSH secretion shows a diurnal rhythm with a surge in the evening. The nocturnal surge is essential for thyroid function regulation. TSH surge is suggested to be blunted in central hypothyroidism. In idiopathic short stature (ISS), thyroid dysfunction has been suggested ranging from mild hypothyroidism to central hypothyroidism.

**Aim of the work**

To study the pituitary thyroid axis and the TSH surge in ISS.

**Materials and methods**

Thirty subjects (10–18 years old) diagnosed as ISS and thirty matched normal controls were chosen for the study. Thyroid function tests were measured in the basal state, namely T₄, T₃, and TSH. TSH was then measured for each subject at 1000, 1900, and 2200 h. A peak nadir levels were determined TSH surge (peak-nadir/nadir) was expressed as percent rise over the nadir.

**Results and conclusion**

33.3% of ISS patients had blunted nocturnal TSH surge (median 10.27) suggesting central hypothyroidism. 33.67% of ISS patients had mild elevation of TSH values and normal nocturnal RSH surge (169.30) suggesting mild hypothyroidism. The remaining 30% of ISS patients had normal thyroid functions and normal nocturnal TSH surge (77.140) as compared to control subjects (60.72) suggesting no role for thyroid dysfunction in this group.

TSH values were lowest at 1900 h in all groups except in mild hypothyroidism at 2200 h. The highest values of TSH were recorded at 2200 h in all groups. The highest values of TSH were recorded at 2200 h in all groups. The highest values of TSH were recorded at 2200 h in all groups.

Addition of ACE inhibitors or ARBs permit to decrease left atrium size and to recover sinus rhythm in 43% of middle aged and 32% of senior patients.

**DO**: 10.1530/endoabs.32.P979

---

**P980**

**Is previous hyperthyroidism associated with long-term cognitive dysfunction? A twin study**

Mads Lillevang-Johansen, Inge Petersen, Kaare Christensen, Laszlo Hegedüs & Thomas Brix

1Department of Endocrinology and Metabolism, Odense University Hospital, Odense, Denmark; 2The Danish Twin Registry, University of Southern Denmark, Odense, Denmark; 3University of Southern Denmark, Odense, Denmark.

**Introduction**

Hyperthyroidism has been suggested to adversely affect cognitive function. However, this association could also be caused by genetic and environmental factors affecting both the development of hyperthyroidism and cognitive functioning. By investigating cognitive function within twin pairs discordant for hyperthyroidism, this potential confounding can be minimized. The aim of this study was to examine if hyperthyroidism is associated with long-term cognitive dysfunction.

**Methods**

Twin pairs discordant for hyperthyroidism were identified by record-linkage between The Danish National Patient Registry, using ICD-8 and ICD-10 codes for hyperthyroidism, and among survey participants of The Danish Twin Registry. Among other investigations, participants had carried out cognitive tests including a Mini-Mental State Exam (MMSE), and six separate cognitive tests. Based on five of the tests a composite cognitive score was calculated. The impact of hyperthyroidism on cognitive function was evaluated by a linear and a conditional logistic regression.

**Results**

Out of 3036 twin pairs were discordant for hyperthyroidism. The mean time from diagnosis until survey participation was 7.3 years (range: 0–24.1 years). In the inter-pair analysis the hyperthyroid group scored significantly better than the healthy group when controlling for sex, age, zygosity, smoking, and comorbidities (linear regression: P=0.038). In the intra-pair analysis the hyperthyroid twin scored significantly better in the MMSE than did the healthy co-twin (paired t-test; P=0.023). When stratifying for time since diagnosis in a paired logistic regression, no statistically significant associations for any of the other cognitive tests were found.

**Conclusion**

Utilizing discordant twin pairs to control for genetic as well as environmental confounding, we could not demonstrate any clinically relevant negative impact of previous hyperthyroidism on long-term cognitive function.

**DO**: 10.1530/endoabs.32.P980

---

**P981**

**The influence of single dose recombinant human thyroid-stimulating hormone on the efficacy of radioiodine therapy in patients with non toxic nodular goitre with low RAIU**

Saeid Abdelrazek, Janusz Mysiwiwcz, Piotr Szymowski, Malgorzata Mojsak, Katarzyna Siewko & Anna Poplawska-Kita

1Department of Nuclear Medicine, Medical University of Bialystok, Bialystok, Poland; 2Department of Endocrinology, Diabetology and Internal Medicine, Medical University of Bialystok, Bialystok, Poland.

**Aim**

The aim of our study was to evaluate the influence of recombinant human thyroid-stimulating hormone (rhTSH) on the efficacy of radioiodine therapy in patients with non toxic nodular goitre with low RAIU.

**Materials and methods**

The study was performed on 50 patients with non toxic nodular goitre (36 females and 14 males, aged 34–75 years) referred for radioiodine therapy. All patients had low RAIU (8–16%), 24 h after a diagnostic dose of 1-131 (4 MBq). All the patients received a single intramuscular dose of 0.05 mg rhTSH (thyrogen). 24 h later diagnostic dose of 1-131 was administered and thyroid scan with RAIU after 24 and 48 h was estimated. Therapeutic dose of 1-131 was given on the third day of rhTSH administration. Serum levels of TSH, fT4 and fT3 were determined, 24 and 48 h after rhTSH administration. Serum levels of TSH, fT4 and fT3 were determined, 24 and 72 h after rhTSH administration and on the 3rd day after radioiodine therapy. The therapeutic activity of 1-131 calculated by Marinelli’s formula and ranged between 280 and 600 MBq. The absorbed dose ranged between 150 and 220 Gy. Follow up control was done every 6 weeks. Thyroid ultrasound, and thyroid scan were done again after 6 and 12 months of radioiodine therapy.

**Results**

A significant increase (2.1 fold) in 24 h RAIU was observed after rhTSH administration. The distribution of radioiodine was more homogeneous 48 h after rhTSH administration. After 12 months 92% of patients were in euthyroid state and 8% develop hypothyroidism. After 6 months the mean reduction in goitre volume was 22 and 45–55% after 12 months. The medium therapeutic activity of 1-131 was 280 MBq.

**Conclusions**

Pre-treatment with rhTSH reduce the therapeutic dose of 1-131 by 50–58% without compromising the result of thyroid volume reduction. rhTSH makes radioiodine therapy more effective in the patients with non toxic nodular goitre with low RAIU.

**DO**: 10.1530/endoabs.32.P981

---

Endocrine Abstracts (2013) Vol 32
PRIMARA: a prospective descriptive observational study to review cinacalcet use in patients with primary hyperparathyroidism in clinical practice

Peter Schwartz1, Jean-Jacques Body2, Jan Cap3, Lorenz Hofbauer4, Mourad Farouk5, Alois Gessl6, Marc Kuhn7, Claudio Maroccio8, Caroline Mattin9, Manuel Munoz Torres10, Juraj Payer11, Ammenienke van de Ven12, Maria Yavropolou13 & Peter Selby14

1Research Center of Ageing and Osteoroposis, Glostrup, Denmark; 2University Hospital Brugmann (Universite Libre de Bruxelles), Brussels, Belgium; 3Carles University, Hradec Kralove, Czech Republic; 4Universitatsklinikum Carl Gustav Carus, Dresden, Germany; 5Amgen Europe, Zurich, Switzerland; 6Medical University of Vienna, Vienna, Austria; 7University Hospital of Rouen, Rouen, France; 8University of Pisa, Pisa, Italy; 9Amgen United Kingdom, Cambridge, UK; 10University Hospital San Cecilio, Granada, Spain; 11Cornelius University and University Hospital, Bratislava, Slovakia; 12Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; 13AHEPA University Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece; 14Institute of Human Development, University of Manchester, Manchester, UK.

PRIMARA is the first observational study to describe the demographic and clinical profiles of adults with primary hyperparathyroidism (pHPT) receiving cinacalcet in daily clinics across European countries. Patients with pHPT aged ≥18 years without prior cinacalcet treatment were eligible. Initial cinacalcet dosage and subsequent dose changes were at the investigator’s discretion. Information on dosing, biochemistry and adverse drug reactions (ADRs) were collected for up to 12 months from enrolment. Analysis was based on observed data. Of 305 patients enrolled, 219 (72%) completed 12 months of cinacalcet treatment; the main reason for cinacalcet discontinuation was parathyroidectomy (40/86; 47%). 303 patients were evaluable for analysis. Forty-four percent were symptomatic with bone pains (43%) and renal stones (37%) reported as the most common symptoms. Reasons for prescribing cinacalcet included: surgery deemed inappropriate (35%), patient declined surgery (28%) or surgery had previously failed or was contraindicated (22%). Cinacalcet mean (s.d.) starting dose was 43.9 (31.8) mg/day. At month 12, 219 subjects (72%) were still receiving cinacalcet dosage and subsequent dose changes were at the investigator’s discretion. A clinically meaningful calcium decline of ≥0.25 mmol/l was observed in 60% of patients. 12 months post cinacalcet initiation without significant safety concerns.

Methods

One hundred and fifty previously untreated subjects with GD (111 female, 39 male, mean age 38.4 ± 12.8 years), 79 with ST (58 female, 21 male, mean age 39.2 ± 14.1 years) and 71 healthy euthyroid controls (43 female, 28 male, mean age 35.8 ± 10.5 years)were included in the study. The diagnosis of GD and ST were made according to the patients’ signs and symptoms, physical examination findings, the results of TRAb and Tc-99m pertechnetate uptake and follow-up findings. All subjects underwent CFDUSG for the quantitative measurement of IMA blood flow velocities.

Results

The mean ITA-PSV and EDV in patients with GD were significantly higher than those with ST (59.0 ± 24.6, 25.2 ± 11.2, 21.4 ± 5.3 and 9.8 ± 2.9 cm/s respectively, P<0.0001 for both comparisons). However, the mean ITA-PSV and EDV were also significantly higher in subjects with ST than controls (21.4 ± 5.3, 9.8 ± 2.9, 17.2 ± 4.4 and 7.6 ± 2.3 cm/s respectively, P<0.0001 for both comparisons).

In ROC analysis the sensitivity/specificity of the 30 and 13.2 cm/s cutoff values of the mean ITA-PSV and EDV for discrimination of GD from ST were 95.39/49 and 89.38/86% respectively. The sensitivity/specificity of the 1.0 IU/l and 3% cutoff values of the TRAb and Tc-99m pertechnetate uptake were 93.0/91.0 and 90.7/89.9% respectively.

Conclusion

This study suggests that the measurement of ITA-PSV by CFDUSG is a useful diagnostic tool for differential diagnosis between GD and ST. In ROC analysis the sensitivity and specificity of the most appropriate cutoff value of the ITA-PSV were higher than the sensitivity and specificity of the the most appropriate cutoff values of TRAb and Tc-99m pertechnetate uptake.

DOI: 10.1530/endoabs.32.P982

P984

Both Graves’ disease and toxic nodular goiter are associated with increased mortality but differ with respect to the cause of death: a Danish population-based register study

Frans Brandt1, Marianne Thvilium1, Dorte Almind2, Kaare Christensen3, Anders Green1, Laszlo Hegeduś1 & Thomas Heiberg Brix1

1Department of Endocrinology and Metabolism, Odense University Hospital, Odense C, Denmark; 2The Danish Aging Research Center and The Danish Twin Registry, University of Southern Denmark, Odense C, Denmark; 3Odense Patient data Exploratory Network, Institute of Clinical Research, University of Southern Denmark, Odense C, Denmark.

Background

Hyperthyroidism has been associated with increased all-cause mortality. Whether the underlying cause of hyperthyroidism influences this association is unclear. Our hypothesis was that Graves’ disease (GD) and toxic nodular goiter (TNG) differ with respect to mortality risk and cause of death.

Methods

An observational cohort study, using record-linkage data from nation-wide Danish health registers. 1,291 and 861 subjects with GD and TNG, respectively, treated in a hospital setting, were identified and followed for a mean period of 11 years. Cases were matched 1:4 with non-hyperthyroid controls with respect to age and sex. The hazard ratio (HR) for mortality was calculated using Cox regression analyses. All analyses were adjusted for co-morbidity, using the Charlson score.

Results

Both GD (HR = 1.42, 95% CI 1.25–1.60) and TNG (HR = 1.22, 95% CI 1.07–1.40) were associated with increased all-cause mortality. After stratification for the cause of death, GD was associated with increased mortality due to cardiovascular diseases (HR = 1.49, 95% CI 1.25–1.77) and lung diseases (HR = 1.91, 95% CI 1.37–2.65), whereas TNG was associated with increased cancer mortality (HR = 1.36, 95% CI 1.06–1.75). When analyzing mortality in GD using TNG individuals as controls, there was no significant difference in all-cause mortality between GD and TNG. However, GD was clearly associated with a higher cardiovascular mortality (HR = 1.39, 95% CI 1.10–1.76) compared to TNG.

Conclusion

Both GD and TNG, treated in a hospital setting, are associated with increased all-cause mortality. The causes of death differ between the two phenotypes with cardiovascular mortality being significantly higher in GD.

DOI: 10.1530/endoabs.32.P984

P983

A comparative study evaluating the roles of inferior thyroid artery blood flow velocities measured by color flow Doppler ultrasonography, TSH receptor antibody and Tc-99m pertechnetate uptake for differential diagnosis between Graves’ disease and silent thyroiditis

Sayid Shafi Zuhur1, Alper Ozel2, Nazan Demir1, Idris Kuzu1 & Yüksel Altuntas1

1Sisli Etfal Training and Research Hospital, Endocrinology and Metabolism Clinic, Istanbul, Turkey; 2Sisli Etfal Training and Research Hospital, Radiology Clinic, Istanbul, Turkey.

Objective

To compare the roles of inferior thyroid artery (ITA) peak systolic and end-diastolic velocities (PSV and EDV) measured by color flow Doppler ultrasonography (CFDUSG), TSH receptor antibody (TRAb) measured by M22 based ELISA and Tc-99m pertechnetate uptake for differential diagnosis between Graves’ disease (GD) and silent thyroiditis (ST).

Both Graves’ disease and toxic nodular goiter are associated with increased mortality but differ with respect to the cause of death: a Danish population-based register study

Frans Brandt, Marianne Thvilium, Dorte Almind, Kaare Christensen, Anders Green, Laszlo Hegeduś & Thomas Heiberg Brix

1Department of Endocrinology and Metabolism, Odense University Hospital, Odense C, Denmark; 2The Danish Aging Research Center and The Danish Twin Registry, University of Southern Denmark, Odense C, Denmark; 3Odense Patient data Exploratory Network, Institute of Clinical Research, University of Southern Denmark, Odense C, Denmark.

Background

Hyperthyroidism has been associated with increased all-cause mortality. Whether the underlying cause of hyperthyroidism influences this association is unclear. Our hypothesis was that Graves’ disease (GD) and toxic nodular goiter (TNG) differ with respect to mortality risk and cause of death.

Methods

An observational cohort study, using record-linkage data from nation-wide Danish health registers. 1,291 and 861 subjects with GD and TNG, respectively, treated in a hospital setting, were identified and followed for a mean period of 11 years. Cases were matched 1:4 with non-hyperthyroid controls with respect to age and sex. The hazard ratio (HR) for mortality was calculated using Cox regression analyses. All analyses were adjusted for co-morbidity, using the Charlson score.

Results

Both GD (HR = 1.42, 95% CI 1.25–1.60) and TNG (HR = 1.22, 95% CI 1.07–1.40) were associated with increased all-cause mortality. After stratification for the cause of death, GD was associated with increased mortality due to cardiovascular diseases (HR = 1.49, 95% CI 1.25–1.77) and lung diseases (HR = 1.91, 95% CI 1.37–2.65), whereas TNG was associated with increased cancer mortality (HR = 1.36, 95% CI 1.06–1.75). When analyzing mortality in GD using TNG individuals as controls, there was no significant difference in all-cause mortality between GD and TNG. However, GD was clearly associated with a higher cardiovascular mortality (HR = 1.39, 95% CI 1.10–1.76) compared to TNG.

Conclusion

Both GD and TNG, treated in a hospital setting, are associated with increased all-cause mortality. The causes of death differ between the two phenotypes with cardiovascular mortality being significantly higher in GD.

DOI: 10.1530/endoabs.32.P984
P985

**Efficacy and safety of combined parenteral and oral steroid therapy in Graves’ orbitopathy**

Biljana Beleslin1, Jasmina Ciric1, Milos Zarkovic1, Marijan Stojašić2, Tanja Ilic1, Boaz Trbojevic1

1Clinic for Endocrinology, Clinical Center of Serbia, Belgrade, Serbia; 2Clinic for Ophthalmology, Clinical Center of Serbia, Belgrade, Serbia.

Introduction

Glucocorticoids (GC) are the first line treatment for moderate-to-severe and active Graves’ orbitopathy (GO), but optimal treatment is still undefined. The aim of the present study was to analyze the efficacy and tolerability of combined parenteral GC pulse therapy followed by oral GC in the interpulse period.

Methods

The study includes 50 patients (48 ± 10 years; 37 females) with untreated, active and moderate-to-severe GO. Patients received 500 mg methylprednisolone in 500 ml physiologic saline followed by oral prednisone tapering dose and repeated each month for the next 5 months. Ophthalmologic assessment was performed before and 6 months after treatment. Side effects of GC therapy were evaluated and recorded each month.

Results

GO showed the greatest effectiveness on soft tissue changes (incorporated in the Results section). Median CAS values decreased from 4.5 to 2.0 (P<0.001). Thirty-seven patients (74%) demonstrated improvement, there was no change in 13 (26%) patients, and none of the patients presented with deterioration of inflammatory status. Diplopia improved in 21 (42%) patients, was unchanged in 28 (56%) patients, and deteriorated in 1 (2%) patient. There was no significant change in the mean values of proptosis (Δ±NS) at the end of treatment. Improvement in optic neuropathy occurred in 56% of patients. At 6 months, 33/50 patients (66%) demonstrated overall treatment response. Side effects occurred in 35/50 (70%) patients, and vast majority of them were mild and minor. Weight gain and hirsutismus were the most common side effects.

Conclusion

With appropriate selection of patients and careful monitoring during and after treatment, combined parenteral and oral GC therapy is effective and safe.

DOI: 10.1530/endoabs.32.P985

---

P987

**Influence of thyrotropin on human peripheral blood immune cell populations**

Mariusz Stasiolek1, zbigniew Adamczewski1,2, Bartosz Puła1, Piotr Dziegiei1 & Andrzei Lewinski1

1Polish Mother’s Memorial Hospital Research Institute, Lodz, Poland; 2Medical University, Lodz, Poland; 3Medical University, Wroclaw, Poland.

Introduction

Dendritic cells (DCs) are considered as main regulators of immune system. Functional properties of DCs depend on their subtype, maturation status, interaction with other immune cells as well as environmental factors including hormones. Recently, we have shown a direct, independent of TSH, regulatory influence of thyroid hormones on human DCs function. The aim of the present study was to analyze ex vivo the effect of systemically administered TSH on human peripheral blood immune cell populations, potentially interacting with DCs and modulating their function.

Methods

Blood samples for the flow cytometry analysis of peripheral blood plasmacytoid and myeloid DC subtypes were collected from patients thyroidectomized because of differentiated thyroid cancer at two consecutive time points: i) directly before the commencement of TSH administration and ii) 5 days after first TSH injection. The whole blood quantitative and phenotypic analysis of immune cell populations was performed by flow cytometry.

Results

As previously shown, systemic administration of TSH did not influence the percentage and maturation status of plasmacytoid and myeloid DCs in peripheral blood of thyroidectomized patients. Interestingly, we observed a significant increase of CD1+ positive PBMCs. This difference was dependent specifically on natural killer (NK) cells whereas the CD16+ monocyte fraction did not change after TSH administration.

Conclusions

In the present study, the systemic TSH administration resulted in the specific increase of CD16+ NK cells fraction in peripheral blood of thyroidectomized patients. These results are of great importance for the understanding of endocrine-immune regulatory network in humans.

DOI: 10.1530/endoabs.32.P987

---

P986

**Type and extent of morbidity before and after the diagnosis of hypothyroidism: a nationwide register-based study**

Marianne Thvilum1, Frans Brandt1, Dorthe Almind2, Kaare Christensen1,2, Laszlo Hegedus1 & Thomas Heiberg Brix1

1Odense University Hospital, Odense, Denmark; 2Department of Clinical Pathology, Naestved Hospital, Region Zealand, Denmark.

Background

Hypothyroidism has been linked with an increased risk of morbidity such as cardiovascular disease and diabetes mellitus. However, it is unknown whether the burden of morbidity is present before or after the diagnosis of hypothyroidism.

Aim

Evaluate the temporality and type of morbidity in hypothyroid patients.

Methods

Observational cohort study. Based on record-linking between official Danish health registers 2822 subjects with hypothyroidism were identified and matched with four non-hypothyroid controls and followed over a mean period of 6 years.

Results

Prevalence of cardiovascular diseases (CVD), lung diseases, diabetes mellitus (DM) and malignant diseases (M) as well as cardiovascular disease and diabetes mellitus. However, it is unknown whether the burden of morbidity is present before or after the diagnosis of hypothyroidism.

Aim

Evaluate the temporality and type of morbidity in hypothyroid patients.

Methods

Observational cohort study. Based on record-linking between official Danish health registers 2822 subjects with hypothyroidism were identified and matched with four non-hypothyroid controls and followed over a mean period of 6 years.

Results

Prevalence of cardiovascular diseases (CVD), lung diseases, diabetes mellitus (DM), rheumatic diseases (RHD) and malignant diseases were recorded. Logistic and cox regression models were used to assess the risk of morbidity before and after the diagnosis of hypothyroidism, respectively.

Results

In subjects with hypothyroidism, the odds ratio (OR) was significantly increased for CVD (OR 1.37; 95% CI: 1.19–1.58), lung diseases (OR 1.25; 95% CI: 1.13–1.39), DM (OR 1.92; 95% CI: 1.61–2.29) as well as malignant diseases (OR 1.24; 95% CI: 1.06–1.45), prior to the diagnosis of hypothyroidism. The hazard ratio (HR) for disease after the diagnosis of hypothyroidism was significantly increased for CVD (HR 1.36; 95% CI: 1.15–1.60), lung diseases (HR 1.51; 95% CI: 1.30–1.75); and DM (HR 1.40; 95% CI: 1.11–1.77).

Conclusions

Prior to the diagnosis of hypothyroidism there is an increased risk of being diagnosed with CVD, lung diseases, DM, and malignant diseases. Following the diagnosis of hypothyroidism there is an increased frequency of CVD, lung diseases, and DM.

DOI: 10.1530/endoabs.32.P986

---

P988

**Hemithyroidectomy for benign euthyroid goiter increases the mitochondrial membrane potential of peripheral mononuclear blood cells**

Tina Toft Kristensen1,6, Jacob Larsen1,6, Palle Lyngsøe Pedersen1,6, Anne-Dorte Feldthues1,6, Stine Anthonsen1,6, Søren Jelstrup1 & Jan Kvetny6

1Department of Otorhinolaryngology, Slagelse Hospital, Region Zealand, Denmark; 2Department of Clinical Pathology, Naestved Hospital, Region Zealand, Denmark; 3Department of Obstetrics and Gynaecology, Naestved Hospital, Region Zealand, Denmark; 4Department of Medicine, Naestved Hospital, Region Zealand, Denmark; 5Mitochondrial Research Unit, Naestved Hospital, Region Zealand, Denmark; 6University of Southern Denmark, Odense, Denmark.

Introduction

Patients who do not develop overt hypothyroidism after hemithyroidectomy for benign euthyroid goiter have permanently increased serum levels of TSH and decreased levels of thyroid hormones within the reference ranges. Thyroid hormones are major regulators of mitochondrial function, and the mitochondrial membrane potential (MMP) can be measured by flow cytometry analysis of living cells as the fluorescence intensity of stained peripheral mononuclear blood cells (MNCs). We have previously shown increased MMP of MNCs in patients with subclinical hypothyroidism. Increased MMP might represent increased production of reactive oxygen species rather than of ATP.

Aim

To determine if the hemithyroidectomy-induced change in TSH and thyroid hormones affects the mitochondria of peripheral MNCs.

Methods

In an ongoing prospective study, patients are examined at one time point before and at four time points (1, 3, 6, and 12 months) after hemithyroidectomy for benign euthyroid goiter. TSH, fT4 and iT3 are measured and the MMP is measured as the fluorescence intensity of stained peripheral mononuclear blood cells (MNCs).

Results

We present a 6-month follow-up of 22 hemithyroidectomized patients who do not receive levothyroxine treatment. TSH shows a persistent increase (median...
0.97 mU/l versus median 2.95 mU/l, P < 0.001), and fT4 (median 16.0 pmol/l vs median 15.20 pmol/l, P < 0.003) and fT3 a persistent decrease (median 1.89 nmol/l vs median 1.73 nmol/l, P < 0.004) within the reference ranges, unchanged to values 1 month after hemithyroidectomy. The MMP of MNBCs was persistently increased after six months (median 4079 TMRM fluorescence a.u. vs median 6327 a.u., P = 0.002).

Conclusion
Although they are considered clinically and biochemically euthyroid, hemi-thyroidectomized patients have lowered thyroid function and hyperpolarized mitochondria. It is unknown if these effects of hemithyroidectomy have clinical consequences.

DOI: 10.1530/endoabs.32.P988

P989
Influence of smoking on hyperthyroidism severity in newly diagnosed Graves’ disease-patients
Sorina Martin1,2, Suzana Florea1 & Simona Fica1,2
1Endocrinology Department, Elias Hospital, Bucharest, Romania; 2Carol Davila’ University of Medicine and Pharmacy, Bucharest, Romania; 3Laboratory Department, Elias Hospital, Bucharest, Romania.

Introduction
Smoking is an independent risk factor for Graves’ disease (GD) and an independent predictor for Graves’ ophthalmopathy (GO), but the influence on hyperthyroidism severity was not established.

Aim
To evaluate the relationship between smoking and thyroid function at diagnosis and after administration of antithyroid drugs (ATDs) in GD patients.

Materials and methods
We prospectively investigated 116 newly diagnosed, untreated GD patients, 82.8% females, mean age 43.8 ± 15.2 years. At diagnosis we recorded: demographic characteristics, smoking status (non-smoker 63.8%, current smoker 36.2%), presence of ophthalmopathy, goiter size, autoantibody titre, serum concentrations of TSH, fT4, fT3, T4, and usual biochemistry. All patients received treatment with methimazole and were followed (mean 12 ± 9 months) at 2 months with physical examination and fT4, fT3, TSH at least until TSH levels returned to normal (>0.4 mU/l). We recorded the time needed for the return of thyroid hormones (THRN) and TSH (THRN) levels to normal.

Results
There was no difference in current smoking percentage between females (33.3%) and males (50%), P = 0.15. Smoker males presented lower fT4 (P < 0.001), higher fT3/fT4 (P < 0.001) at diagnosis and longer THRN (P < 0.001) when compared to non-smoker males. Age at ophthalmopathy onset was significantly lower in current smokers (34.3 ± 11.7 vs 47.9 ± 13.8, P = 0.008), but we found similar percentages of ophthalmopathy between smokers and non-smokers. Smokers > 40 years presented higher fT3 (P = 0.049), fT4 (P = 0.032) and fT3/fT4 (P = 0.034) at diagnosis compared to non-smokers > 40. Compared to nonsmokers, current smokers associated higher prevalence of medium/large goiters (78.6 ± 62.2%, P = 0.025). We found no difference between TSH, fT4, fT3, fT3, antibody titre at diagnosis, the THRN and THRN levels to the return of current smokers and non-smokers

Conclusions
Current smoking is associated with younger age at ophthalmopathy onset, larger goiters, and, generally, does not seem to influence hyperthyroidism severity at diagnosis or the time needed until thyroid hormones and TSH levels return to normal.

DOI: 10.1530/endoabs.32.P990

P991
Quantification of tissue T₃ and T₄ in rat and human heart by novel HPLC-MS/MS method
Alessandro Saba1, Daria Colligiani1, Monica Nannipieri1, Claudia Kusmic2, Cristobal Dos Remedios3, Warner Simonides4, Giorgio Iervasi2 & Riccardo Zucchi2
1University of Pisa, Pisa, Italy; 2CNR Institute of Clinical Physiology, Pisa, Italy; 3University of Sydney, Sydney, New South Wales, Australia; 4VU University Medical Center, Amsterdam, The Netherlands.

Thyroid hormone (T₃) is mostly produced in peripheral tissues by thyroxine (T₄) deiodination, and its functional effects are directly related to tissue concentration, which is quite difficult to assay by conventional immunological methods. We report a novel technique, based on tandem mass spectrometry (MS/MS) coupled to HPLC, which was used in left ventricular myocardium obtained from rat and human hearts. Samples were homogenized in phosphate buffer (pH 7.4). After centrifugation, supernatants were spiked with stable-isotope-labelled internal standards (IS: 12C₃-T₃, 12C₂-T₄ and 13C₃-T₃) and extracted by SPE. Dried residues were reconstituted and incubated with 3.0 N HCl in n-butanol, obtaining the butyl esters of T₃ and T₄. After removing excess reagents, residues were reconstituted with methanol/HCl 0.1 M (50:50 v/v) and injected in the HPLC-MS/MS system (AB-Sciex API 4000). Calibration curves were built with standard solutions containing both analytes at concentrations ranging from 1 to 50 mg/ml and the same amount of IS as put in the samples. Sample derivatization increased method sensitivity and accuracy, and the minimum amount of tissue needed was 100-150 mg. In control rat myocardium, tissue T₃ and T₄ averaged 1.59 ± 0.11 and 2.24 ± 0.22 pmol/g respectively (corresponding plasma free T₃ and T₄ were 3.69 ± 0.39 and 17.09 ± 1.56 pmol/l). In animals treated with low-dose (6 µg/kg per day) or high-dose (45 µg/kg per day) T₃, tissue T₃ increased to 3.12 ± 0.29 and 6.76 ± 1.37 pmol/g.

Table 1 Median values.

<table>
<thead>
<tr>
<th>Table 1 Median values.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoB48</td>
</tr>
<tr>
<td>HDL-C</td>
</tr>
<tr>
<td>HDL2-associated CETP</td>
</tr>
<tr>
<td>HDL3-associated CETP</td>
</tr>
<tr>
<td>FMD% change</td>
</tr>
<tr>
<td>Controls Fasting (n=42)</td>
</tr>
<tr>
<td>SCH Fasting (n=21)</td>
</tr>
<tr>
<td>OH Fasting (n=21)</td>
</tr>
<tr>
<td>Controls Post-ophtalm.</td>
</tr>
<tr>
<td>SCH Post-ophtalm.</td>
</tr>
<tr>
<td>OH Post-ophtalm.</td>
</tr>
</tbody>
</table>

*P < 0.05 vs.controls and **P < 0.001 vs controls.

Postprandial lipoprotein and vascular abnormalities differ between OH and SCH. Although both are characterized by increased intestinally-derived lipoprotein particles, HDL-C is reduced only in SCH. Maintained HDL-C in OH probably reflects reduced CETP, which was not observed in SCH. Postprandial endothelial dysfunction is abnormal only in OH and does not appear to reflect increased inflammation.

DOI: 10.1530/endoabs.32.P990

P990
Postprandial studies uncover differing effects on HDL particles of overt and subclinical hypothyroidism
Anne McGowan1, William M Widdowson1, Anna O’Regan3, Ian S Young3, Gerard Boran2, Jane McEneny3 & James Gibney1
1Department of Endocrinology, Adelaide and Meath Hospital Incorporating the National Children’s Hospital, Tallaght, Dublin 24, Ireland; 2Department of Chemical Pathology, Adelaide and Meath Hospital Incorporating the National Children’s Hospital, Tallaght, Dublin 24, Ireland; 3Centre for Public Health, Queen’s University Belfast, Belfast, UK.

Overt hypothyroidism (OH) and more controversially subclinical hypothyroidism (SCH) are associated with abnormal lipid metabolism and endothelial dysfunction under fasting conditions. Little data exists regarding the metabolic and vascular effects of OH or SCH under postprandial conditions.

We aimed to characterize postprandial metabolism with emphasis on intestinally derived lipoproteins. HDL-cholesterol (HDL-C) and endothelial function in patients with OH, SCH and normal subjects.

Subjects were studied fasting and for 8-h following a mixed-meal. Apolipoprotein (Apo) B48, a marker of intestinally-derived lipoproteins was measured by ELISA. Systemic and HDL-associated inflammation was assessed by measuring serum-amyloid-A (SAA)-levels. HDL was subfractionated into HDL2 and 3 by rapid ultracentrifugation. Cholesteryl-ester-transfer-protein (CETP), which mediates transfer of cholesterol from HDL to triglyceride-rich lipoproteins and LDL-cholesterol (LDL-C) was measured in HDL2 and 3 subfractions. Flow-mediated-dilatation (FMD) of the brachial artery was measured to assess endothelial dysfunction.

Compared to normal subjects, postprandial ApoB48 AUC was greater in OH and SCH while postprandial HDL-C was lower in SCH but not OH. There were no significant between-group differences in LDL-C, triglycerides, or SAA. HDL-2- and 3-associated CETP activity was lower in OH compared to normal and SCH subjects. FMD was reduced in OH compared to SCH and normal subjects postprandially.

Table 1 Median values.

<table>
<thead>
<tr>
<th>Table 1 Median values.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoB48</td>
</tr>
<tr>
<td>HDL-C</td>
</tr>
<tr>
<td>HDL2-associated CETP</td>
</tr>
<tr>
<td>HDL3-associated CETP</td>
</tr>
<tr>
<td>FMD% change</td>
</tr>
<tr>
<td>Controls Fasting (n=42)</td>
</tr>
<tr>
<td>SCH Fasting (n=21)</td>
</tr>
<tr>
<td>OH Fasting (n=21)</td>
</tr>
<tr>
<td>Controls Post-ophtalm.</td>
</tr>
<tr>
<td>SCH Post-ophtalm.</td>
</tr>
<tr>
<td>OH Post-ophtalm.</td>
</tr>
</tbody>
</table>

*P < 0.05 vs.controls and **P < 0.001 vs controls.

Endocrine Abstracts (2013) Vol 32
(plasma free $T_3$ was 8.06 ± 0.83 and 19.59 ± 3.80 pmol/L, while tissue $T_4$ decreased to 0.79 ± 0.06 and 0.77 ± 0.02 pmol/g (plasma free $T_4$ was 6.34 ± 1.41 and 3.49 ± 0.43 pmol/g). In human samples obtained from transplanted hearts $T_3$ and $T_4$ averaged 1.51 ± 0.16 and 5.94 ± 0.63 pmol/g.

In conclusion an HPLC-MS/MS method based on derivatisation with butanol enables $T_3$ and $T_4$ assay in ≥ 150 ng myocardial samples. Tissue $T_3$ and $T_4$ assay may be critical to understand the role of thyroid hormones in physiological and pathophysiological conditions.

DOI: 10.1530/endoabs.32.P991

P992
Study on linear growth and thyroid function for 12 years in patients with β thalassemia major
Ashraf Soliman1, Fawzia Al Yafei1, LoLwa Al-Naimi2, Noora Almarri1, Aml Sabt1, Mohamed Yassun1 & Vincenzo Desanctis2
1Hamad Medical Center, Doha; Qatar, 2Quisisana Hospital, Ferrara, Italy.

Introduction
Short stature and hypothyroidism are frequent complications of thalassemia major (TM).

Patients and methods
We recorder growth parameters and investigated the thyroid function in TM patients attending our Pediatric Endocrine Clinics for 12 years. Definitions: overt hypothyroidism (low FT$_4$ and normal or decreased TSH). (secondary) hypothyroidism (low FT$_4$, TSH between 5–10 mU/l) and central (hypothalamic) hypothyroidism (low FT$_4$ and normal or decreased TSH).

Results
48 patients completed a 12 years of follow-up. Hypothyroidism was diagnosed in 35% of patients without gender difference. There was a progressive decrease of height SDS (from 0.2 ± 0.3 to −1.78 ± 0.5) and BMI SDS (from 0.2 ± 0.3 to −0.6 ± 0.35). HSIDS was <−2 in 46% of patients. The general trend of free thyroxine level showed progressive decrease over the 12 years, whereas TSH levels did not show a corresponding increase. 94% patients had hypothyroidism after the age of 10 years. Overt hypothyroidism had risen from 0% at the age of 7 years to 35% at the age of 18 years. None had high anti-thyroperoxidase (TPO) antibody titers. 13/17 patients with hypothyroidism, had normal or low TSH level (not appropriately elevated) indicative of defective hypothalamic pituitary response to low $T_4$ (central hypothyroidism). 3/17 patients had subclinical hypothyroidism (TSH between 5 and 10 mU/l and normal FT$_4$). There was a significant negative correlation between serum ferritin and FT$_4$ ($r = −0.39$, $P = 0.007$) and between FTS and HTSDS ($r = 0.52$, $P < 0.001$).

Conclusions
Progressive height loss and worsening of thyroid function was observed in 46 and 35% respectively in thalassemic patients by the age of 18 years. The lack of proper increase of TSH in response to low levels of FT$_4$ in (76%) of these patients indicated a high incidence of defective pituitary thyroidic function in these patients.

DOI: 10.1530/endoabs.32.P992

P993
Levothyroxine requirements in thyroidecimized diabetic patients receiving metformin
Carles Zafon, Anna Casteras, Gabriel Obiols & Jordi Mesa
Department of Endocrinology and Nutrition. Hospital Universitari Vall d’Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain.

Background
Recent studies suggest that metformin (MF) may reduce TSH concentration. This fact could imply a dosage reduction of levothyroxine among those hypothyroid patients taking metformin.

Aim
To determine, in a retrospective analysis, the impact of metformin in thyroidecimized patients (a condition not influenced by endogenous thyroid hormone production) on levothyroxine replacement.

Patients and methods
One hundred ninety two subjects underwent total thyroidectomy. Patients were thyroidectomized patients (a condition not influenced by endogenous thyroid hormone production). Replacement dose was properly adjusted in all patients. Levothyroxin requirements were compared between groups.

Results
TSH levels did not show statistically significant differences between the groups: TSH 0.67 (0.11–2.81) mU/l in group B and 0.80 (0.11–4.28) mU/l in group A; $P$ value = 0.46. No differences on total levothyroxine dosage were found: 114 (100–150) μg in group A vs 125 (100–142) in group B; $P$ value = 0.9. However, when calculating the weight adjusted levothyroxine dose (μg/kg) significant differences were evidenced: 1.66 (1.38–2.08) μg/kg in group A vs 1.53 (1.26–1.70) in group B; $P$ value = 0.010. Conclusions
Thyroidectomized patients on metformin treatment do need lower thyroxine dose per kilogram.

DOI: 10.1530/endoabs.32.P993

P994
Association between the use of computed tomography scans using iodine-based contrast medium and the development of subsequent hyperthyroidism
Pernille Holmager1, Henrik Thomsen1 & Jens Faber1
1Department of Endocrinology, Herlev University Hospital, Herlev, Denmark.

Background and aim
There is an increasing use of computed tomography (CT) scans with an iodine-based contrast medium. Last year, a large University Hospital in Denmark performed 50,000 CT scans where each injection contained between 3500 and 7000 μg free iodine corresponding to 23–45 times normal daily intake. We wished to investigate if patients with newly diagnosed hyperthyroidism had been exposed to an iodine based CT scan within 1 year prior to symptoms of hyperthyroidism.

Materials and methods
All patients with newly diagnosed hyperthyroidism (either first time episode or recurrent) through 1 year (2010) were linked individually with a register for CT scans performed in 2009 and 2010. Only cases where a CT scan was performed prior to an outbreak of hyperthyroidism were included.

Results
230 new cases of hyperthyroidism were originally classified as: 101 patients with Graves’ disease (75 new, 28 with recurrent), 72 with multinodular goitre, 9 with amiodarone or iodine-induced hyperthyroidism, 8 with hCG-induced hyperthyroidism, 26 with subacute thyroids, 11 with postpartum thyroiditis, 1 with painless thyroiditis, 1 was Iplimmub-ab induced, and finally 1 induced by Interferon. Fourteen patients, corresponding to 0.0003% of all contrast injections, but 6.1% of all patients with hyperthyroidism, had undergone a CT scan before the outbreak of hyperthyroidism. Based on type of hyperthyroidism, 1/101 (1%) had Graves’ disease, 1/72 (1%) had multinodular goitre and the last two had hyperthyroidism induced by Iplimmub and Interferon.

Conclusion
From a radiologist’s point of view: a CT scan with iodine-based contrast induces extremely seldom hyperthyroidism. From an endocrinologist’s point of view: a CT scan with iodine-based contrast performed within 1 year prior to symptoms seems significantly associated with outbreak of hyperthyroidism in a multinodular gland (15%) as opposed to Graves’ disease.

DOI: 10.1530/endoabs.32.P994

P995
Metformin decreases thyroid volume and nodule size in subjects with insulin resistance
Alptekin Gursoy1, Cuneyd Anil1, Berna Atesagooglu1, Altug Kus1, Asli Nar1 & Neslihan Basci Tuluncu1
1Department of Endocrinology and Metabolism, Faculty of Medicine, Baskent University, Ankara, Turkey.

Introduction
Previous reports have shown that subjects with insulin resistance have increased thyroid volume and nodule prevalence. We investigated the effects of metformin on thyroid volume and nodule size.

Methods
This prospective data were gathered on newly diagnosed subjects with insulin resistance ($n=100$, 68 female, 32 male) between August 2008 and May 2010.

Endocrine Abstracts (2013) Vol 32
Measurements of thyroid hormones and thyroid ultrasonography was performed in all participants before and after 6 months therapy of metformin.

Results
Mean BMI and waist circumference decreased significantly after metformin therapy (34.5±5.1 vs 32.7±4.8 kg/m2 and 106.3±11.8 vs 101.8±19.0 cm respectively) (P<0.001 for BMI; P=0.008 for waist circumference). Insulin resistance estimated by homeostasis model assessment also decreased after metformin therapy (4.5±1.9 vs 2.9±1.7, P<0.0001). After metformin therapy, mean TSH level was lower (1.8±1.0 vs 1.5±0.8 mIU/l, P<0.0001), mean free 

Conclusions
In subjects with insulin resistance, metformin therapy significantly decreases thyroid volume and nodule size, which seems to not only shed light on novel aspects in pathophysiology of goiter, but also to introduce therapeutic challenges as well.

DOI: 10.1530/endoabs.32.P9955

A case of severe hypoglycaemia in a patient with hyperthyroidism
Pranjali Patwari1, Anirudhan Narasimhan1 & Ramalingam Srinivasan1,2
1GI Kuppusamy Naidu Memorial Hospital, Coimbatore, Tamilnadu, India; 2Endocrine Society of Coimbatore, Coimbatore, Tamilnadu, India.

Introduction
Graves’ disease is a common condition which is usually treated with antithyroid drugs such as carbimazole and propylthiouracil. Here we present a patient who developed severe hypoglycaemia after treatment with carbimazole for hyperthyroidism which is unusual in Indian population.

Case report
A 31-year-old male Indian presented to Endocrine Clinic with typical signs and symptoms of thyrotoxicosis. His biochemistry showed FT4 28.16 pmol/l (1.8–4.6), T3 20.5 ng/dl (0.93–1.7), TSH: 0.005 mIU/l (0.27–4.2) and random blood sugar was 90 mg/dl. Technetium thyroid scan showed high uptake of 13.4% and Graves’ disease was confirmed, following which he was treated with carbimazole and propranolol. Two weeks later the patient presented to hospital with unconsciousness, frothy discharge from mouth, seizures and sweating. Severe hypoglycaemia confirmed with blood sugar of 29.2 mg/dl. In the hospital he had repeated episodes of hypoglycaemia which was treated symptomatically. Further investigation revealed normal cortisol level but his inulin level was elevated at repeated episodes of hypoglycaemia which was treated symptomatically. According to presence (group A) or absence (group B) of urinary phthalate metabolites participants divided in two groups. Free thyroxin (FT4), free triiodothyronine (FT3) and thyroid-stimulating hormone (TSH) were measured. Phthalate monoester metabolites (MEP-monoethyl phthalate, MBP-monobuthyl phthalate, MOP-mono-(2-ethylhexyl)-phthalate) were measured in single spot urine by mass spectrometry.

Results
In all groups values of thyroid hormones and TSH were in normal range (FT4 13.41 ± 1.49 pmol/l, FT3 5.00 ± 0.64 pmol/l, TSH 1.87 ± 2.98 mIU/l). Urine phthalate metabolite values were: MEP 36.40 ± 137.46; MBP 22.94 ± 118.34; MOP 16.43 ± 102.01; MEHP 44.55 ± 83.30 mg/ml. Significant negative correlation were between FT4 and MEP (r = −0.214, P<0.05) and significant positive between TSH and MEP (r=0.444; P<0.01). In group A values of FT4 and FT3 were slightly decreased and TSH increased than in group B. Urine values of phthalate metabolites in group A were: MEP 71.21 ± 186.65; MBP 22.94 ± 118.34; MOP 16.43 ± 102.01; MEHP 44.55 ± 83.30 mg/ml. Significant positive correlation were found between FT4 and MEP (r = −0.300; P<0.05) and borderline between FT4 and MEP (r = 0.282; P=0.06). Statically significant positive correlation was between TSH and MEP (r =0.542; P<0.01).

Conclusion
Exposure to DEP (diethylphthalate) may affect thyroid function. Further studies are needed to elucidate this association.

DOI: 10.1530/endoabs.32.P997

Associations between urinary phthalate metabolites and thyroid function: pilot study
Milica Medić-Stojanoska1,2, Nataša Milić, Jovanka Novaković-Paro1,4, Ivana Bajkić1,4, Tijana Ičin1,4, Andrijana Milankov1, Djordje Popović1,3, Branka Kovačev-Zavić1,4 & Nikola Ćurić1,4
1Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of Vojvodina, Novi Sad, Vojvodina, Serbia; 2Department of Pharmacy, Medical School Novi Sad, Novi Sad, Vojvodina, Serbia; 3Institute of Laboratory Medicine, Clinical Center of Vojvodina, Novi Sad, Vojvodina, Serbia; 4University of Novi Sad Medical School, Novi Sad, Vojvodina, Serbia.

Background
Phthalates presents widespread endocrine disrupting chemicals in many personal-care and consumer products. A limited number of experimental and human studies suggest that exposure to phthalate may be associated with altered thyroid hormone, but a problem is not elucidated enough. This study focused to examination of the association between urine phthalate metabolites and thyroid function.

Methods
We included 91 healthy person, 47 females and 44 males, mean age 35.91 ± 8.10 years. According to presence (group A) or absence (group B) of urinary phthalate metabolites participants divided in two groups. Free thyroxin (FT4), free triiodothyronine (FT3) and thyroid-stimulating hormone (TSH) were measured.

Results
In all groups values of thyroid hormones and TSH were in normal range (FT4 13.41 ± 1.49 pmol/l, FT3 5.00 ± 0.64 pmol/l, TSH 1.87 ± 2.98 mIU/l). Urine phthalate metabolite values were: MEP 36.40 ± 137.46; MBP 22.94 ± 118.34; MOP 16.43 ± 102.01; MEHP 44.55 ± 83.30 mg/ml. Significant negative correlation were between FT4 and MEP (r = −0.214, P<0.05) and significant positive between TSH and MEP (r=0.444; P<0.01). In group A values of FT4 and FT3 were slightly decreased and TSH increased than in group B. Urine values of phthalate metabolites in group A were: MEP 71.21 ± 186.65; MBP 22.94 ± 118.34; MOP 16.43 ± 102.01; MEHP 44.55 ± 83.30 mg/ml. Significant positive correlation were found between FT4 and MEP (r = −0.300; P<0.05) and borderline between FT4 and MEP (r = 0.282; P=0.06). Statically significant positive correlation was between TSH and MEP (r =0.542; P<0.01).

Conclusion
Exposure to DEP (diethylphthalate) may affect thyroid function. Further studies are needed to elucidate this association.

DOI: 10.1530/endoabs.32.P997
P999

Short-term effects of thyroid hormone therapy on quality-of-life evaluation by ThyPRO questionnaire in chronic autoimmune thyroiditis
Marilena Sidoti1,2 & Massimo Giusti1,2
1Centro Diagnostico Piamar, Savona, Italy; 2Dipartimento di Medicina Interna, Università di Genova, Genoa, Italy.

In chronic autoimmune thyroiditis, increased TPOAb levels have been found to be associated with impaired quality-of-life (QoL). Aim of the study was to evaluate ThyPRO, a QoL questionnaire of patients with positive TPOAb levels. From January to December 2011, 62 women were invited to the study. Inclusion criteria were: age > 18 years, TPOAb > 100 mIU/l, no previous therapy for thyroid, no current wish to become pregnant and availability of an E-mail address. Women

P1000

Genetic examination of the TSHR gene in patients with congenital hypothyroidism: systematic survey of a Hungarian cohort
Arpad Labadzi1,2, Balázs Gellén1, Beáta Ruza1, Oroszly Rideg2, Gábor L Kovács1, Ennese Mezős1 & Luca Persani4
11st Department of Internal Medicine, University of Pécs, Pécs, Hungary; 2Pediatrics Department, University of Szeged, Szeged, Hungary; 3Department of Laboratory Medicine, University of Pécs, Pécs, Hungary; 4Division of Endocrinology and Metabolic Disease, Laboratory of Endocrine and Metabolic Research, Italian Aulxovou Institute, Milan, Italy.

Loss-of-function mutations in the TSH receptor (TSHR) gene are one of the most common known causes of congenital hypothyroidism (CH). While heterozygous mutations result in nonautoimmune isolated hyperthyrotropinemia, homozygous and compound heterozygous mutations may cause overt CH of various severity depending on the localization and type of the mutations. In our study we performed the systematic genetic analysis of the TSHR gene of a cohort of 85 Hungarian patients diagnosed postnatally with CH in Szeged, one of the two Hungarian centres involved in the neonatal TSH screening program. Patients’ detailed clinical data were collected and DNA was isolated from peripheral blood. Genetic analysis was implemented at the Division of Endocrinology and Metabolic Disease, Laboratory of Endocrine and Metabolic Research, Italian Auxlovou Institute, as follows. Exons and their immediate flanking intronic sequences were PCR amplified. Examination of the resulting PCR fragments were performed either with denaturing HPLC (DHPLC), or with direct sequencing, where it was appropriate. In those cases, where DHPLC result indicated genetic alteration, sequencing was also performed. As a result, beside polymorphic variants, we identified six missense mutations in four patients, among which two mutations are new, so far unidentified naturally occurring mutations (N432D and P449L). Patients 24 and 79 harboured heterozygous mutations (N432D and P162A respectively), whereas Patients 52 and 58 were compound heterozygotes (P162A–P449L and C41S–P162A respectively).

As all four patients had overt CH, genetic examination of the post-transcriptional regulatory elements of the TSHR gene in the heterozygous patients may be also considered. These results along with future genetic examination of the patients’ families, as well as the in vitro functional studies of the new mutations may help us deciphering further details of the complex signalling mechanism through TSHR.

DOI: 10.1530/endoabs.32.P999

P1001

In pregnant women receiving levothyroxine, higher 3rd trimester TSH and maternal underweight are associated with cesarean section due to foetal malposition
Inka Milambres1, Anna Aulinina1, Marta Claramonte2, Sonia Martinez2, Apolonia García-Patterson3, Juan María Adelantado4 & Rosa Corcoy1
1Endocrinology and Nutrition Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; 2Endocrinology, Gynecology and Obstetrics Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain.

Context
In the background population, maternal TSH levels > 2.5 mIU/l in late pregnancy have been reported to be associated with breech presentation. This has not been addressed in women treated with levothyroxine.

Aim
Our aim was to study the relationship of 3rd trimester maternal TSH with caesarean section (CS) due to foetal malposition in pregnant women treated with levothyroxine since before pregnancy.

Methods
We have studied 222 women with primary pregestational hypothyroidism or differentiated thyroid carcinoma treated with levothyroxine since before pregnancy and delivering at a gestational age of 22 weeks or more. Women with pregestational diabetes mellitus and multiple pregnancies were excluded. As potential predictors of CS due to malposition we have considered 3rd trimester TSH, maternal age, BMI classification, nulliparity, gestational age at delivery, foetal sex, birth weight, small/adequate/large weight for gestational age, and major malformations. Statistical analyses: data are expressed as percentage or median (P25, P75), analyses include a logistic regression analysis with CS due to foetal malposition as the dependent variable and using all the previously mentioned potential predictors.

Results
Maternal characteristics were age 33 (30–36) years, prepregnancy BMI 23.33 (21.4–23.8) kg/m2, mean 3rd trimester TSH 1.5 (0.3–2.6). The most frequent underlying diseases were hypothyroidism (50%), hypothyroidism after treatment for Graves’ disease (27.6%) and post-surgery differentiated thyroid carcinoma (15.3%). The rate of CS due to foetal malposition was 2.7%. Logistic regression analysis to predict CS due to foetal malposition identified 3rd trimester maternal TSH and maternal underweight as potential predictors, with odds ratios of 1.29 (1.1–1.5) and 13.9 (1.17–165.5) respectively.

Conclusions
In women receiving pregestational treatment with levothyroxine, maternal 3rd trimester TSH and underweight are predictors of CS due to foetal malposition. This extends the findings in the general obstetric population.

DOI: 10.1530/endoabs.32.P1001

P1002

Diagnosis of hypothyroidism is associated to an increased risk of acute decompensated heart failure occurrence, but not of mortality among heart failure outpatients
Vincenzo Triggiani1, Massimo Iaccovelli2, Agata Pazzovolos2, Valeria Antoncecchi2, Vito Angelo Giagulli1, Edoardo Guastamacchia1 & Stefano Favel1
1Unit of Endocrinology, Department DIM, University of Bari, Bari, Italy; 2Unit of Cardiology, Department DETO, University of Bari, Bari, Italy.

It has been demonstrated that hypothyroidism could affect the prognosis of patients with cardiovascular disease. The aim of this study was to better clarify the prognostic role of hypothyroidism in patients with chronic heart failure (CHF).

We enrolled 384 consecutive outpatients (65 ± 13 years, 296 males, NYHA 2.3 ± 0.6, left ventricular ejection fraction, LVEF, 32 ± 9%) with CHF (ESC criteria), in stable clinical conditions (at least 30 days) and in conventional

DOI: 10.1530/endoabs.32.P1002
Thyroid dysfunction has been linked to reduced fertility. It is known that changes in SHBG and sex steroids are a consistent feature associated with hyper- and hypothyroidism. It is also has reported that women with polycystic ovary syndrome (PCOS) are more insulin-resistant than it would be expected on the basis of their age and BMI. The mechanisms underlying this phenomenon are still not clarified. Hyperandrogenaemia may play a role, but also other factors such as thyroid function may also be involved. The aim of this study was to estimate the basis of their age and BMI. The mechanisms underlying this phenomenon are still not clarified. Hyperandrogenaemia may play a role, but also other factors such as thyroid function may also be involved. The aim of this study was to estimate the basis of their age and BMI. The mechanisms underlying this phenomenon are still not clarified. Hyperandrogenaemia may play a role, but also other factors such as thyroid function may also be involved. The aim of this study was to estimate the basis of their age and BMI. The mechanisms underlying this phenomenon are still not clarified. Hyperandrogenaemia may play a role, but also other factors such as thyroid function may also be involved. The aim of this study was to estimate the basis of their age and BMI. The mechanisms underlying this phenomenon are still not clarified. Hyperandrogenaemia may play a role, but also other factors such as thyroid function may also be involved. The aim of this study was to estimate the basis of their age and BMI. The mechanisms underlying this phenomenon are still not clarified. Hyperandrogenaemia may play a role, but also other factors such as thyroid function may also be involved. The aim of this study was to estimate the basis of their age and BMI. The mechanisms underlying this phenomenon are still not clarified. Hyperandrogenaemia may play a role, but also other factors such as thyroid function may also be involved. The aim of this study was to estimate the basis of their age and BMI. The mechanisms underlying this phenomenon are still not clarified. Hyperandrogenaemia may play a role, but also other factors such as thyroid function may also be involved. The aim of this study was to estimate the basis of their age and BMI. The mechanisms underlying this phenomenon are still not clarified. Hyperandrogenaemia may play a role, but also other factors such as thyroid function may also be involved. The aim of this study was to estimate the basis of their age and BMI. The mechanisms underlying this phenomenon are still not clarified. Hyperandrogenaemia may play a role, but also other factors such as thyroid function may also be involved. The aim of this study was to estimate the basis of their age and BMI. The mechanisms underlying this phenomenon are still not clarified. Hyperandrogenaemia may play a role, but also other factors such as thyroid function may also be involved. The aim of this study was to estimate the basis of their age and BMI. The mechanisms underlying this phenomenon are still not clarified. Hyperandrogenaemia may play a role, but also other factors such as thyroid function may also be involved. The aim of this study was to estimate the basis of their age and BMI. The mechanisms underlying this phenomenon are still not clarified. Hyperandrogenaemia may play a role, but also other factors such as thyroid function may also be involved. The aim of this study was to estimate the basis of their age and BMI. The mechanisms underlying this phenomenon are still not clarified. Hyperandrogenaemia may play a role, but also other factors such as thyroid function may also be involved. The aim of this study was to estimate the basis of their age and BMI. The mechanisms underlying this phenomenon are still not clarified. Hyperandrogenaemia may play a role, but also other factors such as thyroid function may also be involved. The aim of this study was to estimate the basis of their age and BMI. The mechanisms underlying this phenomenon are still not clarified. Hyperandrogenaemia may play a role, but also other factors such as thyroid function may also be involved. The aim of this study was to estimate the basis of their age and BMI. The mechanisms underlying this phenomenon are still not clarified. Hyperandrogenaemia may play a role, but also other factors such as thyroid function may also be involved. The aim of this study was to estimate the
**P1005**

**TSH-deficiency is associated with a lower thyroid gland volume in hypopituitaric patients compared to healthy volunteers: a cross-sectional study**

Danielle Santì1,2, Giulia Brigante1,2, Valentina Gnaini1,2, Bruno Masedo1,2, Sara De Vincentis1,2, Cesare Carani1,2, Marco Faustini-Fustinì1, Antonio Balestrieri1 & Vincenzo Rocchi1,2

1Chair and Unit of Endocrinology and Metabolism, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy; 2Integrated Department of Medicine, Endocrinology and Metabolism, Geriatrics, Azienda USL of Modena, NOCSAE of Baggiovana, Modena, Italy; 3Endocrine unit, Department of Medicine, Bellaria Hospital, Bologna, Italy; 4Endocrinology and Metabolism Unit, Department of medicine, Ospedale ‘M. Bufalini’, Asl of Cesena, Cesena, Italy.

### Results

One hundred and eleven of them were using medications containing L-thyroxine (57.5%). IGF1 levels of 179 patients (92.8%) were normal. Fourteen patients had insulin resistance, hepatosteatosis, hypothyroidism, hyperthyroidism. We decided that patients with hepatosteatosis and either hypothyroidism or 48% (P, nonsignificant), respectively. HOMA-IR indices were not statistically different between groups (P = 0.104). Conclusions Hypothyroidism and hyperthyroidism are not correlated to insulin resistance in patients with hepatosteatosis. We decided that patients with hepatosteatosis already have insulin resistance despite different associated comorbidities. Similar studies in literature did not emphasize on hepatosteatosis in such cases. Key words Insulin resistance, hepatosteatosis, hyperthyroidism, hyperthyroidism. DOI: 10.1530/endoabs.32.P1007

---

**P1006**

**Prevalence of GH deficiency in Turkish patients with Hashimoto’s thyroiditis: a single center experience**

Safak Akin1, Kadiye Aydin1 & Alper Gurlek2

1Safak Akin, Ankara, Turkey; 2Kadiye Aydin, Ankara, Turkey; 3Alper Gurlek, Ankara, Turkey.

### Background and Aim

Prevalence of Hashimoto’s thyroiditis is increasing in Turkey. GH deficiency has been reported to associate with this disorder in several different ethnic population. The aim of this study was to evaluate GH deficiency in the population with Hashimoto’s thyroiditis.

### Results

One hundred ninety three patients with Hashimoto’s thyroiditis were evaluated (136 males, 267 females) (47.2 ± 11.63 years). All subjects underwent thyroid ultrasonography (Siemens Acuson Antares, Philadelphia, USA) performed by the same operator. TV was calculated as the sum of TV of the two lobes, each estimated as: length (cm) × width (cm) × depth (cm) × 0.52.

**Results:***

Age, weight, BMI and body surface area (BSA) were greater in hypopituitaric patients than healthy volunteers. Thyroid nodules were incidentally discovered at ultrasonography in 17 hypopituitaric (29.3%) and 93 volunteers (38.1%). TV was lower in hypopituitaric patients than in volunteers (6.066 ± 3.079 ml, P < 0.001). This difference was also confirmed in the subgroup without nodules (mean 4.719 ± 3.230 and 9.430 ± 3.497 ml, P < 0.001), but not when comparing hypopituitaric patients and volunteers with goiter. Finally, TV was lower in hypopituitaric patients without nodules (4.73 ± 3.27 ml) than in those with goiter (9.62 ± 7.18 ml; P = 0.003). These differences were held even after correction of TV for BSA, BMI and age.

### Discussion

TV is significantly lower in hypopituitaric patients than in healthy subjects, but the prevalence of thyroid nodules seems to be similar. The reduction of TV in hypopituitaric patients seems to occur only in thyroid glands without nodules. The chronic lack of TSH, as in hypopituitarism, seems to be responsible in vivo for a reduction of TV, but this effect seems to involve mainly the normal thyroid tissue rather than the hyperplastic nodular tissue.

DOI: 10.1530/endoabs.32.P1006

---

**P1007**

**Insulin resistance in patients with thyroid dysfunction and hepatosteatosis**

Sakir Ozgur Keskek, Sinan Kırım, Ramazan Kaya, Dilek Tuzun, Gulay Ortolgu & Tayyibe Saler

Numune Education and Research Hospital, Adana, Turkey.

### Introduction

Hepatosteatosis is one of the results of insulin resistance. Thyroid dysfunctions effect on insulin sensitivity. The aim of this study was to evaluate insulin resistance in patients with hepatosteatosis and either hypothyroidism or hyperthyroidism.

### Design

A total of 407 patients with hepatosteatosis were included. These patients were further divided into two study subgroups and a control group: 102 subjects with hypothyroidism, 103 with hyperthyroidism and 202 with normal thyroid function in the control group. The institution review board of hospital approved the study. Serum TSH, free T4, free T3 concentrations, blood glucose, and insulin levels, serum lipid levels, hepatic transaminases and homoeostasis model assessment of insulin resistance (HOMA-IR) were measured. Insulin resistance was calculated according to HOMA-index and compared between the groups. IBM Statistics 20.0 for Windows was used for statistical analysis. χ² and ANOVA tests were used for comparing groups.

### Results

Average age was 50.8 ± 14.1 years. Male:female ratio was 141:266. Frequencies of insulin resistance in patients with hepatosteatosis and either hypothyroidism, hyperthyroidism, or normal thyroid function were 43, 40, and 48% (P, nonsignificant), respectively. HOMA-IR indices were not statistically different between groups (P = 0.104).

### Conclusions

Hypothyroidism and hyperthyroidism are not correlated to insulin resistance in patients with hepatosteatosis. We decided that patients with hepatosteatosis already have insulin resistance despite different associated comorbidities. Similar studies in literature did not emphasize on hepatosteatosis in such cases.

### Key words

Insulin resistance, hepatosteatosis, hypothyroidism, hyperthyroidism.

DOI: 10.1530/endoabs.32.P1007

---

**P1008**

**Vitamin D status in autoimmune hypothyroidism**

Sunil Kumar Kotas1,2, Lalit Kumar Meher1,2, Sruti Jammula1,3 & Kirtikumar D Modi1,3

1Medwin Hospital, Hyderabad, Andhrapradesh, India; 2MKCG Medical College, Berhampur, Orissa, India; 3Roland Institute of Pharmaceutical Sciences, Berhampur, Orissa, India.

### Objective

To investigate vitamin D status in patients with autoimmune hypothyroidism.

### Methods

The study group consisted of 100 patients with newly diagnosed Hashimoto’s thyroiditis and 100 subjects as the control group. Parameters of calcium metabolism, thyroid function tests and 25(OH) vitamin D levels were measured. Results or case presentation

Mean age of the study groups was 33.4 ± 4.8 years with female:male, 72:28. Vitamin D insufficiency/deficiency (25(OH)D < 30 ng/ml) rate was significantly higher in the Hashimoto’s group compared with the control subjects (75 vs 20%, P < 0.0001). In the Hashimoto group, mean 25(OH) vitamin D levels were significantly lower compared with the control group (12.5 ± 7.0 vs 22.3 ± 7.9 ng/ml, P < 0.001). The study group revealed

DOI: 10.1530/endoabs.32.P1008
Conclusion
The higher vitamin D deficiency rates besides lower vitamin D levels in the Hashimoto group together with the inverse correlation between vitamin D and anti-TPO suggest that vitamin D deficiency may have a role in the autoimmune process in Hashimoto’s thyroiditis.

DOI: 10.1530/endoabs.32.P1008

P1009
Vascular endothelial growth factor and granulocyte–monocyte colony stimulating factor levels in nodular thyroid diseases

Birsen Bilgici, Gulcin Ecemis, Ozgur Tuncel, Ilkay Bayrak, Elif Kan & Aysegul Atmaca
Ondokuz Mayis University, Samsun, Turkey.

Introduction
Vascular endothelial growth factor (VEGF) is a specific mitogen for endothelial cells. Granulocyte–monocyte colony stimulating factor (GM-CSF) is a key player in the regulation of steady-state functions. Studies have shown increased levels of VEGF and GM-CSF in benign and malignant tumors. The aim of this study was to evaluate the relation between VEGF and GM-CSF levels and thyroid nodules >1 cm, and negative for malignancy with fine needle aspiration biopsy (FNAB). Methods and design
Forty-one female patients with benign euthyroid nodular goiter were enrolled as the patient group and 20 age-matched healthy women without thyroid disease were enrolled as the control group. Age, serum VEGF, serum GM-CSF, TSH, fT3, fT4, anti-thyroglobulin (anti-TG) antibody, anti-thyroid peroxidase (anti-TPO) antibody and thyroid volume were compared between the patient and control group.

Results
Only thyroid volume and anti-TG levels were significantly different between the two groups (P = 0.007, P = 0.026 respectively). Other parameters including VEGF and GM-CSF were not significantly different. Serum VEGF levels were positively correlated with anti-TPO levels in the patient group (r = 0.325, P = 0.036). No correlations were found between VEGF and other parameters. Serum GM-CSF levels were not correlated with any parameters.

Conclusions
VEGF and GM-CSF were not found to be increased in euthyroid patients with benign nodules and they do not seem to play a role in the development of simple nodular goiter. However, correlation between serum VEGF levels and anti-TPO levels in the patient group may indicate a relation between VEGF and development of autoimmune thyroid diseases as suggested by some authors.

DOI: 10.1530/endoabs.32.P1009

P1010
Increased TRAb and/or low anti-TPO titers at diagnosis of Graves’ disease (GD) are associated with an increased risk of developing ophthalmopathy after onset of GD

Mikael Lantiz, Tereza Planck, Peter Asman & Bengt Hallengren
Department of Clinical Sciences, Skåne University Hospital, Lund University, Malmö, Sweden.

Objective
Patients with low thyroid peroxidase antibodies (anti-TPO) and increased TSH-receptor antibodies (TRAb) at diagnosis of Graves’ disease (GD) have been suggested to have an increased risk to develop Graves’ ophthalmopathy (GO). The aim was to evaluate if GO development can be predicted.

Design
Observational study with registration of possible GD and GO risk factors.

Methods
Three hundred and ninety nine patients with GD were registered 2003–2008 in Malmö, Sweden and out of these 310 were retrospectively followed up to 6 years.

The main outcome measures were anti-TPO titer, TRAb titer, smoking habits, radioiodine treatment, and GO development.

Results
TRAb was assessed with a third generation assay at GD diagnosis in 231 patients. The proportion of patients with GO increased above the median 6.3 IU/l both at diagnosis of GD (P = 0.001) and at follow-up (P = 0.001).

The distribution of GO patients anti-TPO above or below 20 kIU/l at diagnosis of GD was similar between groups (P = 0.239). However at follow-up anti-TPO < 20 kIU/l was associated with an increased proportion of newly developed GO as compared to the cohort with anti-TPO > 20 kIU/l (P = 0.018).

Eighty seven percentage of patients who developed GO after GD diagnosis had TRAb above 6.3 IU/l and/or anti-TPO below 20 kIU/l. The proportion of GO was doubled in GD patients treated with radioiodine but could not explain the described findings.

Conclusions
Anti-TPO < 20 kIU/l and/or TRAb > 6.3 IU/l at the time of GD diagnosis were associated with an increased risk to develop GO after diagnosis of GD.

DOI: 10.1530/endoabs.32.P1010

P1011
Latent toxoplasmosis: a novel risk factor for autoimmune thyroid diseases in pregnancy?

Eliska Potlukova1, Lucie Prochazkova2, Jan Jiskra2, Zdenka Limanova1, Drahomira Springer1, Pavel Calda1, Jaroslav Plega3 & Sanka Kankaova1
3Third Department of Medicine, General University Hospital, Prague, Czech Republic; 2Faculty of Science, Charles University, Prague, Czech Republic; 1Institute of Clinical Biochemistry and Laboratory Diagnostics, Prague, Czech Republic; 4Clinic of Gynaecology and Obstetrics, General University Hospital, Prague, Czech Republic.

Introduction
Latent toxoplasmosis, a zoonosis caused by protozoan Toxoplasma gondii, is the most widespread human parasitosis in developed countries (prevalence 20–80%). Upon infection, T. gondii stays in human organism lifelong. It has been linked to several autoimmune diseases, including autoimmune thyroid disease (AITD). The aim of our study was to assess the impact of latent T. gondii infection on the prevalence of AITD in pregnancy with regard to the pregnancy outcome.

Methods
We assessed the presence of latent toxoplasmosis by using complement-fixation reaction and ELISA-measurement of IgG and IgM antibodies in serum of 1247 consecutive pregnant women in 9th–11th gestational weeks. Two women suspected from acute toxoplasmosis were excluded from the study. We determined serum levels of autoantibodies against thyroid peroxidase (TPOAb) (upper cut-off limit for the first trimester of pregnancy was 143 kU/l) and TSH in the same serum sample. In 592 women, data on pregnancy outcome were available (after exclusion of twin-pregnancies).

Results
The overall prevalence of latent toxoplasmosis among was 22.6%. Women with high elevation of TPOAb (> 500 kU/l) suffered from latent toxoplasmosis more frequently than women with TPOAb < 500 kU/l (36.8 vs 21.8%, P = 0.007). This effect wasn’t present when the cut-off 143 kU/l was used. Serum levels of TPOAb correlated with the toxoplasma IgG-index of positivity (P = 0.009, r = −0.077).

We didn’t find any effect of latent toxoplasmosis on TSH in TPOAb-positive women. However, among the TPOAb-negative ones, those positive for T. gondii had significantly lower TSH values (1.53 vs 1.240 mU/l, P = 0.017). Women with latent toxoplasmosis didn’t have an increased prevalence of complications during pregnancy or adverse pregnancy outcomes.

Conclusions
Latent toxoplasmosis is frequent in pregnancy and it may increase the risk of AITD. However, it is not linked to adverse pregnancy outcomes.

DOI: 10.1530/endoabs.32.P1011

P1012
Iodine status in women after early miscarriages in the Czech Republic

Jan Jiskra1, Tom´iˇs Fait1, Radovan Bilek1, Jana Bart´akova1, Eliska Potluková1, Drahomira Springer1, Zdenka Telicka1 & Zdenka Limanova1
13rd Clinic of Medicine, 1st Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic; 2Department of Gynaecology and Obstetrics, 1st Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic; 1Institute of
Early miscarriages are of multifactorial origin. Subclinical thyroid dysfunction belongs to the common causes. Thyroid dysfunction in pregnancy is caused mainly by thyroid autoimmunity and/or iodine deficiency. The Czech Republic belongs to countries with sufficient iodine intake. The aim of the study was to determine iodine status in women after early miscarriages (n = 183) and to compare it with randomly chosen age-comparable euthyroid women without previous pregnancy (controls, n = 118).

Subjects and methods
A total of 183 consecutive women after miscarriage in the 9-12th weeks of pregnancy were included in the study. Within 3 months after miscarriage, we performed a laboratory assessment of urinary iodine concentration (UIC; absorption spectrophotometry) and an evaluation of the thyroid function including thyroid ultrasound. Seventy-two women were supplemented by iodine in previous pregnancy, 73 were not and in 38 the information wasn’t available.

Results
Women after miscarriages had a significantly lower median of UIC as compared to controls (92 vs 108.6 μg/l, P<0.001). Furthermore, only 72/183 (39.3%) of women after miscarriage had sufficient iodine intake (UIC ≥100 μg/l) as compared to 71/118 (60.2%) in controls (P<0.001). In the rest of the samples analysed, we noted mild (UIC 50–99 μg/l) and moderate iodine deficiency (UIC 20–49 μg/l) without significant differences among the groups (57.9 vs 39.8% and 2.7 vs 0% respectively). None of the women analysed suffered from severe iodine insufficiency (UIC <20 μg/l). There were no significant differences in UIC between women supplemented with iodine in the previous pregnancy as compared to those who weren’t.

Conclusions
Czech women after miscarriages suffer from mild or moderate iodine deficiency significantly more often than healthy women without history of pregnancy. Our data support iodine supplementation in women attempting pregnancy even in iodine-sufficient countries.

DOI: 10.1530/endoabs.32.P1012

P1013
An open-label, randomized, controlled study of the effectiveness and safety of a high intensity focused ultrasound device compared with observation in patients with non-malignant cold thyroid nodules

Laurence Leenhardt1, Agnes Rouxel1, Fabrice Menegaux2 & Olivier Esnault2
1Pitie Salpetriere, University Paris 6, Paris 75013, France; 2ENT and cervicofacial Surgery, Paris 75017, France.

Aim
To compare nodule volume change at 6 months follow-up in patients treated by ultrasound guided high intensity focused ultrasound (US-HIFU) with patients undergoing observation in a simple monocentric, open label, randomized-control study.

Patients and methods
The study was IRB approved and all patients signed an informed consent. 32 patients with 34 benign cold thyroid nodules indicated for surgery were recruited for the study: 21 patients assigned to the HIFU arm and 11 patients/13 nodules to the observation arm. Nodule volume was assessed by US and thyroid function determined by routine assays before and during follow-up. The presence and severity of pressure symptoms and cosmetic complaints were also evaluated. Safety was assessed in all patients during the study period.

Mean age was 49±12 years. Median HIFU duration was 54 min (32–114). The overall median energy deposited was 25 kJ (0.8–79).

Results
At M6, the mean decrease in volume was 1.1 ml (−5.5 to 1.7) and 0.3 ml (−1.1 to 3.7) in the HIFU group and the observed group respectively. (P=0.0223).
In the HIFU group five patients experienced a volume reduction of over 30% (40.4–82) compared with zero patients in the observed group. At baseline, 66% of the treated patients and 45% of the observed patients had pressure symptoms. At 6M only 23.8% of the treated patients were still having pressure symptoms while no change was recorded in the observed patients. One transitory vocal cord palsy occurred just after HIFU ablation but disappeared within 14 days. After that incident, the device was equipped with a safety feature. Side effects were restricted to mild local pain after the HIFU session. Thyroid function remained unaltered.

Conclusion
HIFU is safe in benign cold thyroid nodule treatment. Its promising impact on nodule volume reduction and pressure symptoms needs to be evaluated on a larger scale.

DOI: 10.1530/endoabs.32.P1013

P1014
Biochemical testing on wide indication to detect overt hypothyroidism is justified: a population-based case–control study in patients newly diagnosed with overt autoimmune hypothyroidism

Allan Carlé1, Inge Bülow Pedersen1, Nils Knudsen1, Lars Ovesen1, Lone Banke Rasmussen2, Torben Jørgensen3, Hans Perrild4 & Peter Laurberg5, 6
1Department of Endocrinology and Medicine, Aalborg University Hospital, Aalborg, Denmark; 2Endocrine Unit, Medical Clinic I, Bispebjerg Hospital, Copenhagen, Denmark; 3Department of Internal Medicine, Slagelse Hospital, Slagelse, Denmark; 4Ministry of Food, Agriculture and Fisheries, National Food Institute, Technical University of Denmark, Copenhagen, Denmark; 5Research Centre for Disease Prevention and Health, Copenhagen, Denmark; 6Faculty of Health Science, University of Copenhagen, Copenhagen, Denmark; 7Faculty of Medicine, University of Aalborg, Aalborg, Denmark.

Objectives
Hypothyroid patients report a diversity of symptoms at disease presentation. We studied how useful symptoms are to predict hypothyroidism, and if this may vary between subgroups of patients.

Methods
Patients newly diagnosed with overt autoimmune hypothyroidism (n=140) were prospectively identified in a population by linkage to diagnostic laboratory databases, and we concomitantly enrolled individually sex and age-region matched controls (n=560). Patients and controls participated in a comprehensive investigational program including the presence of 36 symptoms. Sensitivity and diagnostic odds ratios (DOR, >1 significant, >10 very useful as a diagnostic tool) were calculated. In multivariate models, we identified predictors for presence of each symptom. Subgroup analysis was performed in three age groups (tertiles, group A/B/C=0–48.1 years/48.1–58.2 years/58.2 years).

Results
13 of 36 symptoms were more frequent (DOR >1) among patients than in controls. DOR was highest for tiredness (5.94 (3.70–9.60 (95% CI)), feeling unwell (4.10 (2.57–6.54), hair loss (4.58 (2.80–7.71)), and dry skin (2.73–6.16). Tiredness and feeling unwell were independent of age, but age was a predictor for globulus sensation (only present in the two younger age groups (+/+/+)), swelling difficulties (+/+/+/+), anterior neck pain (+/+/+/+), restlessness (+/+/+/+), cardiac palpitations (+/+/+/+), bad mood (+/+/+/+), constipation (+/+/+/+), decreased appetite (+/+/+/+), hair loss (+/+/+/+), dry skin (+/+/+/+), and vertigo (+/+/+/+). Serum T4 (T4, not TSH or T3) was predictor for degree of tiredness, smoking for shortness of breath. No difference was observed between sexes, regions investigated, or alcohol intake level.

Conclusions
Symptom presentation did not differentiate very well between cases and controls, with great overlap especially in elderly people. Interestingly, symptoms were more closely associated with age at presentation than with the biochemical degree of hypothyroidism at debut. Biochemical testing on wide indication to diagnose overt hypothyroidism is justified.

DOI: 10.1530/endoabs.32.P1014

P1015
Associations of (FT₃) and the ratio FT₃:FT₄ with a cluster of obesity-related cardiovascular risk markers in healthy euthyroid middle-aged men and women

Greet Roel1, Ernst Rietzschel2, Caroline Van Daelc2, Youri Taes3, Marc De Buyzere2, Thierry Gilibe1 & Jean-Marc Kaufman2
1Department of Endocrinology, Ghent University Hospital, Ghent, Belgium; 2Department of Cardiovascular Diseases, Ghent University, Ghent, Belgium.

Background
We have previously shown that a higher BMI and less favorable body composition are associated with relatively higher FT₃ levels (within the euthyroid range) in healthy young men. In this study, we aimed to investigate whether FT₃ and the ratio FT₃:FT₄ are also associated with cardiovascular markers in a healthy euthyroid population of middle-aged men and women.

Endocrine Abstracts (2013) Vol 32
Methods
Thyroid parameters were measured in 2524 subjects from the Asklepios Study (35–55 years). Analyses were restricted to 2315 subjects (1138 women and 1177 men), not using thyroid medication nor having anti-TPO levels above clinical cut-off or TSH levels outside the reference range (0.27–4.2 mU/l). Thyroid function parameters were determined by automated electrochemiluminescence. Statistical analysis was performed by linear and logistic regression analysis in SPSS.

Results
(FT3) and the ratio FT3:FT4 were significantly positively related to BMI and waist circumference (both P<0.001) and other elements of the metabolic syndrome, i.e. triglycerides, systolic and diastolic blood pressure and fasting plasma glucose (all P values <0.001). (FT3) and the ratio FT3:FT4 were also associated with lower HDL-levels (P<0.001). The presence of the metabolic syndrome as a whole (both according to the IDF as the ATPIII-criteria) was also related to higher (FT3) levels and a higher FT3:FT4 ratio (OR = 2, P < 0.0001). All the associations regarding the metabolic syndrome remained significant after adjustment for sex, age, height, weight or waist circumference, and smoking. The FT4:FT3 ratio was further positively associated with obesity-related predictors of cardiovascular events: elevated IL6 (> 1.5 pg/ml; OR = 1, P = 0.001) and elevated hs-CRP (> 3 mg/l; OR = 1.7, P = 0.001), even after adjustment for sex, age, height, weight or waist circumference, and smoking.

Conclusion
In healthy euthyroid middle-aged men and women, higher (FT3) levels and a higher FT3:FT4 ratio are associated with a cluster of obesity-related cardiovascular risk markers. However, no causal inferences can be made from this cross-sectional study.

DOI: 10.1530/endoabs.32.P1015
Conclusion
AIT presents a specific hormonal profile, which reflects the effects of AMD on thyroid hormones metabolism: significantly lower FT$_4$ ($P=0.01$) and higher FT$_3$ ($P=0.29$), as compared to endogenous hyperthyroidism.

DO: 10.1530/endoabs.32.P1018

P1019
Differential item functioning of the thyroid-specific quality of life questionnaire ThyPRO
Torquil Watt$^{1,2}$, Laszlo Hegediüs$^{2}$, Steen Jørg Bonnema$^{2}$, Jakob Bue Bjørner$^{2}$, Mogens Groenvold$^{3}$, Åse Krogh Rasmussen$^{4}$ & Ulla Feldt-Rasmussen$^{4}$
$^1$Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark; $^2$Odense University Hospital, Odense, Denmark; $^3$University of Copenhagen, Copenhagen, Denmark; $^4$National Research Centre for the Working Environment, Copenhagen, Denmark.

Objectives
Thyroid diseases have been shown to affect quality of life. A thyroid-specific patient-reported outcome (PRO) measuring quality of life, the ThyPRO, has recently been developed and validated using classical clinic- and psycho-metric methods. The purpose of the present study was to apply modern psychometrics to validate the measure as the extent of differential item functioning (DIF) according to sex, age, education and diagnosis, within the ThyPRO.

Methods
Eight hundred and thirty eight patients with benign thyroid diseases (non-toxic goitre, toxic nodular goitre, Graves’ hyperthyroidism, Graves orbitopathy and autoimmune hypothyroidism) completed the ThyPRO questionnaire (84 five-point items, 13 scales). Uniform and non-uniform DIF was investigated using ordinal logistic regression, testing for both statistical significance and magnitude ($\Delta$Res $>0.02$).

Results
Twenty instances of DIF were found. Seven according to diagnosis, where the goitre scale was the most affected scale, possibly due to differing perceptions in patients with autoimmune thyroid diseases compared to patients with simple goitre. Eight age-related DIFs were found, five of which were in positively worded items, which younger patients were more likely to endorse; one gender-related where men were more likely to report crying, and three according to educational level. The vast majority of DIFs only had minor influence on the scale scores (0.1–2.3 points on the 0–100 scales), but two DIFs corresponded to a difference of 4.6 and 9.8 respectively.

Conclusion
Ordinal logistic regression identified DIF in 17 of 84 items. The potential impact of this on the present scales was low, but the results can assist the planning and interpretation of future clinical trials. Shorter and more clinically implementable versions of the ThyPRO would be of virtue in the future, and items displaying DIF could be avoided when developing such abbreviated scales, where the impact of one items with DIF among fewer items will be larger.

DOI: 10.1530/endoabs.32.P1019

P1020
Insulin resistance in patients with hypothryoidism or hyperthyroidism without hepatosteatosis
Sakir Ozgur Kesek, Sinan Kirim, Mehmet Tasdemir, Dilek Tuzun, Galay Ortagli & Tayyibe Saler
Numune Education and Research Hospital, Adana, Turkey.

Introduction
Insulin resistance, refers to decreased response of tissues to insulin, primarily associated with type 2 diabetes and glucose intolerance. Several results were obtained in previous studies about the relation between insulin resistance and thyroid dysfunction. In these studies hepatosteatosis was not an exclusion criteria despite insulin resistance has a key role in the development of it. In this study we aimed to investigate insulin resistance in patients with hyperthyroidism or hypothyroidism without hepatosteatosis.

Design
A total of 340 patients without hepatosteatosis were included. These patients were further divided into two study subgroups and a control group: 106 subjects with hyperthyroidism, 104 with hypothyroidism, and 130 with normal thyroid function in the control group. The institution review board of hospital approved the study. We measured serum TSH, free T$_4$, free T$_3$, concentrations, blood glucose and insulin levels, serum lipid levels, hepatic transaminases, and homeostasis model assessment of insulin resistance (HOMA-IR). Insulin resistance was calculated according to HOMA index and compared between the groups. SPSS 19.0 Package Program (SPSS, Inc.) was used for statistical analysis. $\chi^2$ and ANOVA tests were used for comparing groups.

Results
Average age of 340 patients was 41.2 ± 10.9 years. Male:female ratio was 52:288. Frequencies of insulin resistance in hypothyroidism, hyperthyroidism or normal thyroid function were 17, 20, and 24% ($P=0.073$) respectively. HOMA-IR indexes were $1.85 \pm 1.18$, $1.96 \pm 1.54$, $2.09 \pm 1.79$ respectively. The difference was not statistically significant. ($P=0.589$).

Conclusion
In this study, we did not found insulin resistance in patients with hypothyroidism or hyperthyroidism. We concluded that insulin resistance could be associated with comorbidities in patients with thyroid dysfunction in previous studies. In our opinion, hepatosteatosis should be evaluated as a comorbidity in such patients.

Key words
Insulin resistance, hypothyroidism, hyperthyroidism, hepatosteatosis.

DOI: 10.1530/endoabs.32.P1020

P1021
Should subclinical hypothyroidism diagnosed during pregnancy be treated with long-term i-thyroxine?
Bijay Vaidya$^{1,2}$, Bea Knight$^2$, Anita Hill$^2$, Andrew Hattersley$^{1,2}$ & Beverley Shields$^2$
$^1$Royal Devon and Exeter Hospital, Exeter, UK; $^2$Exeter University, Exeter, UK.

Background
Subclinical hypothyroidism is common in pregnancy affecting about 5% of all pregnant women, and is associated with adverse pregnancy outcomes. There is a general consensus that subclinical hypothyroidism detected during pregnancy should be treated with l-thyroxine (Stagnaro-green et al. 2011, DeGroot et al. 2012). However, it is unclear whether the treatment should be limited only during the pregnancy or continued long-term. Therefore, we aimed to study whether subclinical hypothyroidism detected during pregnancy is reversible after pregnancy.

Subjects and methods
We analysed TSH, free T$_4$, free T$_3$ and thyroid peroxidase antibodies (TPO-Ab) on stored serum samples from 988 women at 28 weeks pregnancy. We carried out same tests on 523 of these women, who had no known thyroid disease or overt hypo- or hyperthyroidism during the pregnancy, on a visit mean (S.D.) 4.9 (1.6) years after delivery.

Results
Subclinical hypothyroidism in pregnancy (defined as TSH $>$3 mU/l for third trimester; Stagnaro-Green et al. 2011, DeGroot et al. 2012) was present in 65/523 (12.4%) of women. Of these, 48 (74%) women had normal thyroid function post-pregnancy; only 14 (21.5%) had persistently high TSH (defined as TSH $>$4.5 mU/l post-pregnancy) and a further 3 (4.6%) were on l-thyroxine. Those with TPO-Ab $>$20 IU/ml had higher TSH above 5 mIU/l ($P=0.03$) in pregnancy were more likely to have persistently elevated TSH or be on l-thyroxine replacement outside pregnancy. 45/523 (8.6%) of patients had isolated maternal hypothyroxinaemia in pregnancy (defined as free T$_4$ below 10th centile without raised TSH). Only 2 (4.4%) of them had raised TSH outside pregnancy. The proportion of women with positive TPO-Ab more than doubled post-pregnancy compared to that in pregnancy (12 vs 5%).

Conclusions
The majority of cases of subclinical hypothyroidism in pregnancy are transient, so treatment of l-thyroxine in these cases may not be warranted outside of pregnancy.

DOI: 10.1530/endoabs.32.P1021

P1022
IgG4-related Hashimoto’s thyroiditis: an emerging variant of a well known disease
Henriquez Lait, Diogo Gonçalves, Bernardo Pereira, Tiago da Silva, Andreia Veloza, Catarina Matos, Isabel Manita, Maria Cordeiro, Luisa Raimundo, Ana Oliveira, Maria Brito & Jorge Portugal
Garcia de Orta Hospital, Almada, Portugal.

Introduction
IgG4-related Hashimoto’s thyroiditis (HT) is a very recently reported entity, characterized by thyroid inflammation rich in IgG4-positive plasma cells associated with marked fibrosis. It may be part of the systemic IgG4-related
sclerosing disease and is associated with younger age, lower female: male ratio, higher levels of thyroid autoantibodies, low echogenicity on ultrasound (US), rapid progress requiring surgery and more subclinical hypothyroidism, when compared with non-IgG4 HT.

Case report
A 56-year-old man presented with a 4-month history of progressive neck swelling, dysphagia, and weight loss of 7 kg. Cervical palpation identified an enlarged, hard and painless thyroid gland. Laboratory testing revealed: increased ESR, 81 mm/h (<31) and CRP, 8.2 mg/dl (<1), normal free T4, 0.99 ng/dl (0.93–1.7) and very high levels of anti-Tg, > 4000 IU/ml (<40) and anti-TPO, >600 IU/ml (<35). US demonstrated an enlarged and heterogeneous thyroid gland, with a substantial component, both lobes with maximal dimension >10 cm and two hypoechoic nodules with 3.2 and 2.2 cm located on the isthmus and right lobe, respectively. US-guided fine needle aspiration cytology was performed and the material removed from both nodules was consistent with lymphocytic thyroiditis. The patient was submitted to total thyroidectomy with no surgical complications. Histological findings showed lymphoplasmacytic infiltration, lymphoid follicles with germinal centers and marked fibrosis limited within the thyroid capsule; an increased number of IgG4-positive plasma cells was found by immunohistochemistry. One month after surgery, serum IgG4 concentration was high-normal, 165 mg/dl (3–201). Symptoms relief and reduction in laboratory inflammatory parameters were noticed. Thyroid function was controlled with levothyroxine.

Conclusions
We report a typical case of IgG4-related HT. The presentation form suggested the diagnosis, which was confirmed based on histological data. Our case highlights this new variant of the well known HT, and helps physicians in recognizing its main clinical features.

DOI: 10.1530/endoabs.32.P1022

P1023
Prevalence of thyroiditis in ankylosing spondylitis patients
Korhan Bars Basayram, Ece Hanman, Serkan Akcay, Serpil Bai & Banu Arslan
1Department of Endocrinology, Izmir Ataturk Training and Research Hospital, Izmir, Turkey; 2Department of Physical Therapy and Rehabilitation, Izmir Ataturk Training and Research Hospital, Izmir, Turkey; 3Department of Orthopedics and Traumatology, Izmir Ataturk Training and Research Hospital, Izmir, Turkey; 4Department of Biochemistry, Izmir Ataturk Training and Research Hospital, Izmir, Turkey.

Objective
We aimed to evaluate the prevalence of thyroiditis in ankylosing spondylitis patients in this study. We investigated the role of serum procalcitonin as a chronic inflammatory marker in ankylosing spondylitis.

Methods
Sixty-seven patients who diagnosed as ankylosing spondylitis according to American College of Rheumatology (ACR) criteria and 57 healthy controls were included in our study. Serum levels of procalcitonin, TSH, free triiodothyronine (FT3), free thyroxine (FT4), anti thyroglobulin (anti-TG) and antithyroid peroxidase (anti-TPO) were measured in both groups. The presence of thyroiditis and nodules were evaluated by ultrasonography of the thyroid gland. The disease activity of ankylosing spondylitis were evaluated by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).

Results
There were no significant differences in terms of thyroiditis between patients and control groups. It was not detected correlation between serum procalcitonin level and BASDAI in patient group. It was shown that there was no correlation among serum procalcitonin levels, the presence of nodules, and thyroiditis. But, there was a correlation between thyroiditis and serum procalcitonin levels in control group (P<0.05).

Table 2 Evaluation of serum procalcitonin levels between the groups.

<table>
<thead>
<tr>
<th></th>
<th>Patient group</th>
<th>Healthy control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>Procalcitonin levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroiditis present</td>
<td>0.09±0.03</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Thyroiditis absent</td>
<td>0.08±0.04</td>
<td>0.05±0.25</td>
</tr>
<tr>
<td>Nodules present</td>
<td>0.09±0.05</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Nodules absent</td>
<td>0.08±0.03</td>
<td>0.07±0.13</td>
</tr>
</tbody>
</table>

Conclusion
Although some studies in the literature that showing a significantly higher prevalence of thyroid otoimmunity in patients with spondyloarthritides, we could not show such a relationship in our study. Furthermore, serum procalcitonin concentration was elevated in some cases of thyroiditis. However, it was not shown a relation between procalcitonin and ankylosing spondylitis which was one of chronic inflammatory diseases.

Key words
Ankylosing spondylitis, procalcitonin, thyroiditis.

DOI: 10.1530/endoabs.32.P1023

P1024
The study of gastrointestinal hormones in patients with hypothyroidism of middle-aged and elderly
Gulnur Moldabek, Zhangelkhan Abylayuly & Alma Mansharipova
Kazakhstan National Medical University, Almaty, Kazakhstan.

The purpose of study was to examine the content of gastrointestinal hormones in patients with hypothyroidism.

Objectives and methods
We investigated of 37 patients, which hypothyroidism, at the age from 23 to 65 years. The diagnosis of hypothyroidism was confirmed by measurement of thyroid hormones and TSH in serum. Immunohistochemistry in gastrobiopsies of the antrum of patients studied gastrin, serotonin, melatonin. The primary antibodies used commercial antibodies to serotonin, gastrin, melatonin (Dako Glostrup, Denmark, caption 1:50). Measurements were conducted in five fields of view (objective with increase in 40) in three slices of the examined organ.

Results
In the group of patients in whom no biopsy serotonin and melatonin in the blood TSH level was 19.9 ± 3.8 mIU/l, the level of free thyroxine (T4) of 7.8 ± 2.3 pmol/l, total T4 8.1 ± 3.8 ng/ml. In the group of patients whose biopsy visually determined serotonin in the blood TSH level was 14.38 ± 2.4 mIU/l, the level of free T4 of 8.1 ± 2.3 pmol/l, total T4 47 ± 4.9 ng/ml. Only in biopsies of patients with hypothyroidism were detected all young gastrointestinal hormones: gastrin-secreting cells (G-cells) 5.6 ± 3.7%, serotonin-secreting cells (EC-cell) 3.7 ± 1.3%, melatonin-producing cells 1.3 ± 0.6%. Given results testify about the disturbance in the system of local hormonal gastrointestinal regulation, close interrelation of disturbances (GIG) with the vegetative nervous system.

Conclusion
Thus, the results indicate a possible violation of local gastrointestinal hormonal regulation in patients with hypothyroidism with middle-aged and elderly.

DOI: 10.1530/endoabs.32.P1024
The study of levels erythropoietin and proinflammatory cytokines in patients with hypothyroidism of different ages
Gulnar Moldabek
Kazanu, Almaty, Kazakhstan.

Objectives
The aim of study was to examine the levels erythropoietin in hypothyroidism with anemic syndrome of different ages.

Methods
We investigated 52 patients with hypothyroidism with iodinedeficiency normochromic and hypochromic anemia. Among them were 21 patients between ages from 21 to till 45 years old and 31 over 45 years of age. Examination included total blood, in the blood levels of thyroid hormones, serum iron, erythropoietin, ferritin by standard methods.

Results
As a result it was found that 38% of patients with Hb levels of the blood was below 70 g/l and 62% of patients with Hb levels was below 90 g/l between ages from 21 to till 45 years old. So, it was found that patients over 45 years of age 19% have Hb levels of the blood was below 70 g/l and 81% patients below 90 g/l.

Conclusion
Thus, in hypothyroidism with anemia, a change of proinflammatory cytokines and decreased levels of erythropoietin and ferritin showed an increase in proinflammatory cytokines IFNγ up to 7.15 ± 2.3 pg/ml and IL1β 11.4 ± 5.2 pg/ml that testifies to suppression of the level of erythropoietin by interleukins. In the analysis of thyroid function in patients with hypothyroidism with anemia it was found that the level of TSH was within 23.7 ± 2.8 mIU/ml and free T4 7.9 ± 1.3 pg/ml, antibodies to thyroid peroxidase 327.5 ± 62.7 IU/ml.

DOI: 10.1530/endoabs.32.P1025

Acute renal failure as the first presentation of severe hypothyroidism
Cuneyd Anil1 & Aysegul Oruc2
1Department of Endocrinology and Metabolism, Yozgat State Hospital, Yozgat, Turkey; 2Department of Nephrology, Yozgat State Hospital, Yozgat, Turkey.

Introduction
Renal impairment associated with hypothyroidism without any other clear underlying cause is relatively rare. We report a case with severe hypothyroidism admitted with acute renal failure.

Case report
A 72 years old female patient was admitted to the emergency department with progressively worsening complaints of fatigue, somnolence, and swellings all over her body for the last 3 weeks. Initial laboratory examination revealed acute renal failure (BUN: 150 mg/dl, creatinine: 5.03 mg/dl) after which she was hospitalized. Past history disclosed no previous thyroid disease, thyroid medication, or thyroid surgery. History about any renal disease was also unrevealing. She did not receive any statin or fibrate therapy. She only received ramipril for hypertension for about 1 year. She did not receive any thyroid medication. She had no history of diabetes.

On physical examination, she was hypothermic and had periorbital, facial, and lower extremity edema. The thyroid gland was not palpable. She was apathetic. Laboratory analysis revealed: Anemia with Hb 7.2 g/dl, WBC 5,200 with differential count NGWBC 55%, lymphocytes 32%, monocytes 9%, eosinophils 2%, and platelets 275,000. Total bilirubin 5.1 mg/dl, AST 46 IU/l, ALT 22 IU/l, ALK-phos 126 IU/l, Na 135 mEq/l, K 4.1 mEq/l, Cl 101 mEq/l, Ca 8.9 mEq/l, PO4 4.8 mg/dl, Mg 2.2 mEq/l, glucose 115 mg/dl. The serum electrolyte, uric acid, urate, serum protein, albumin, and globulin levels were normal. Serum tSH was 200 mIU/ml and fT3 1.00 pg/ml and high creatine phosphokinase levels with normal MB fraction suggesting rhabdomyolysis. Thyroid autoantibody levels were positive. Autoantibody screening for systemic autoimmune disease and complement levels were normal. Ultrasoundography was negative for blood and protein in the urine. Ultrasonography of thyroid revealed nontoxic goiter. Radioiodine uptake was 30% and serum TSH and fT4 level 5.2 pg/ml and 100 mIU/ml. BUN was 80 mg/dl, creatinine 2.3 mg/dl and creatinine clearance 37 ml/min. The level of erythropoietin in blood plasma in 71% of patients was below 5 ng/ml. As a result, it was found that 38% of patients with Hb levels of the blood was below 70 g/l and 62% of patients with Hb levels was below 90 g/l.

Conclusion
Hypothyroidism may be a cause or triggering factor of acute renal failure. Thyroid function tests may become part of the routine list to go through as a cause of acute renal failure.

DOI: 10.1530/endoabs.32.P1026

Thyroid diffuse lipomatosis: a rare and benign disease
Eva Lau1,2, Paula Freitas1,2, Frederica Gonçalves2,3, Joana Pardal4, Catarina Eloy4,5, Luis Matos-Lima4 & Davide Carvalho1,2
1Departments of Endocrinology, Diabetes and Metabolism, Centro Hospitalar São João, Oporto, Portugal; 2Faculty of Medicine, Centro Hospitalar São João, Oporto, Portugal; 3Surgery, Centro Hospitalar São João, Oporto, Portugal; 4Pathology, Centro Hospitalar São João, Oporto, Portugal; 5Institute of Pathology and Immunology Molecular, University of Porto, Oporto, Portugal.

Introduction
Diffuse lipomatosis of the thyroid is a very rare disease, characterized by extensive infiltration of thyroid parenchyma by mature adipose tissue. It is not accompanied by accumulation of amyloid fibrils.

Clinical report
Male, 47 years old, followed in Endocrinology by hypothyroidism, since 13 years old, medicated with levothyroxine, with unremarkable growth and psicometor development. In 2002, thyroid echography showed a solid and heterogeneous lesion (6.6×3.3 cm size), suggestive of a lipomatosis formation. Fine needle biopsies were always inconclusive. In 2010, CT and MRI showed the same cervical lipomatosis lesion (15×6, 5×4, 9 cm), occupying the entire thyroid anatomic region and extending till the retropharyngeal space. Microbiopsy revealed: ‘fibro-fatty tissue surrounding regular thyroid follicles’. Surgical excision of the neck mass showed an extensive infiltration of the thyroid parenchyma by mature adipose tissue without atypia. These morphological findings and the history of subtotal thyroidectomy by thyroid nodule at 3 years of age with identical histological characteristics have allowed the diagnosis of diffuse lipomatosis of the thyroid gland.

Conclusion
The pathophysiology of adipose tissue infiltration in the thyroid gland is not clear. The definitive treatment is surgery and most of the lesions are benign. The prognosis is favourable.

DOI: 10.1530/endoabs.32.P1027

Regression of ophthalmopathic exophthalmos in Graves’ disease after thyroideotomy: an observational study in a surgical series
Panchangam Ramakanth Bhargav
Care Hospital, Khammam, India.

Background
Ophthalmomaphic exophthalmos is reported to favourably regress after total thyroideotomy compared to radio-iodine or antithyroid drug therapy. This is a prospective study of 15 patients of Graves’ disease associated with ophthalmomaphic exophthalmos. Preoperative and monthly postoperative evaluation of exophthalmos was done with Hertel’s exophthalmometer with a minimum follow up of the cohort was 12 months.

Results
F:M ratio was 12:3 and mean age = 33.4 years (18–55). Exophthalmos was bilateral in 13 and unilateral in two patients. Exophthalmos regressed in 12 patients at mean follow-up of 8 months (2–14) and was static in 3. Mean regression of exophthalmos was 2.2 mm (1–5). The regression was statistically significant at P value = 0.04.

Conclusions
Graves’ disease associated exophthalmos regresses in 73% of cases with significant symptomatic relief, after thyroideotomy. Total thyroideotomy appears to be an ideal management for Graves’ disease associated with ophthalmomaphic exophthalmos.

Key words
Graves’ disease; Ophthalmopathy; Exophthalmos; Total thyroideotomy; Regression.

DOI: 10.1530/endoabs.32.P1028
Vitamin E supplementation in the treatment of Graves’ disease

Mirela Sanda Petrulea¹, Ioana Ilie¹, Ana Valea¹, Cristina Ghervan¹, Carmen Georgescu¹, Cezar Login², Adriana Muresan² & Ileana Duncen¹
¹Department of Endocrinology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania; ²Department of Physiology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania.

Hyperthyroidism in the course of Graves’ disease leads to intensification of oxidative processes resulting in increased oxidative stress.

Objectives

The effect of supplementation with vitamin E was monitored on the speed of attaining euthyroidism and on the oxidative stress parameters in patients with Graves’ disease, treated with thiamazole.

Patients and methods

We examined 43 hyperthyroid patients and 12 euthyroid healthy controls. Patients were divided into two groups according to the treatment: Thiamazole + Metoprolol group and Thiamazole + Metoprolol + vitamin E (Vit E) group.

Results

Patients who received supplementation with vitamin E in addition to therapy with thiamazole (Group 2) attained euthyroidism faster than the patients treated with only thiamazole (Group 1). The marker of lipid peroxidation, carbonyl proteins and reduced glutathione (GSH) were determined from the serum, twice, before the treatment and after 4 weeks of therapy.

Conclusions

The results of the study clearly indicate that supplementation with antioxidants in the treatment of Graves’ disease is justified, particularly those containing vitamin E. Nutritional antioxidants as pharmacological compounds may represent an innovative therapeutic approach to hyperthyroidism as a combined treatment with antithyroid drugs.

DOI: 10.1530/endoabs.32.P1029

Radioiodine treatment of hyperthyroidism in the elderly

Teresa Azevedo, Teresa Martins, João Neto, Sofia Oliveira, Eugénia Revora & Fernando Rodrigues
IPO-Coimbra, Coimbra, Portugal.

Introduction

Treatment of hyperthyroidism in older adults is crucial to reduce its morbidity and mortality. Radioactive iodine has been widely used in this age group due to its availability, safety and cost-effectiveness.

Aim

To determine the efficacy of ¹³¹I for treatment of hyperthyroidism in the elderly.

Methods

Retrospective study of 86 hyperthyroid patients aged ≥65 years who performed radioiodine therapy. We evaluated the following parameters: gender, age, thyroid disease, clinical, and laboratory situation at 1, 3, and 5 years after treatment. We excluded 22 patients who didn’t have a minimal follow-up of 1 year.

Results

We evaluated 64 patients (89% females) with a mean age (± s.d.) of 74.4 ± 6.4 years (range 65–89 years) at the time of radioiodine treatment. Twenty-eight patients (44%) had toxic multinodular goiter, 27 (42%) had toxic adenoma and 9 (14%) had Graves’ disease. We documented hyperthyroidism, subclinical in most cases, in 27% (17/63), 12% (5/42), and 6% (2/32) of patients at 1, 3, and 5 years after radioiodine therapy, respectively. The prevalence of hyperthyroidism was 10% (6/63), 24% (10/42), and 38% (12/32) at 1, 3, and 5 years after treatment with ¹³¹I respectively. Euthyroidism was observed in 63% (40/63), 64% (27/42), and 56% (18/32) after 1, 3, and 5 years of follow-up, respectively. Seven patients (11%) needed two and one patient (1.6%) needed three doses of radioiodine to solve the hyperthyroidism. One patient underwent surgery. There were no significant complications due to radioiodine therapy.

Conclusion

Radioiodine therapy has proved to be effective and safe to control hyperthyroidism in this age group. The cell necrosis induced by radioiodine occurs gradually hence its effect may not be achieved immediately.

DOI: 10.1530/endoabs.32.P1030

The influence of subclinical hypothyroidism on glucose levels

Vesna Popovic Radinovic¹, Zorica Basic Milutinovic¹, Jelena Tica Jevtic¹, Marina Vujovic², Zoran Gluvic², Milena Jackovic² & Maja Stojadinovic Ilic²
¹Clinical Hospital Center Zemun, Beograd, Serbia; ²High Health-Sanitary School of Professional Studies, Beograd, Serbia.

Background

Recently many authors are questioning the existing of elements of metabolic syndrome (MetSy) in patients with subclinical hypothyroidism (SH). In this cross sectional study we observed glycaemia, as an element of MetSy, in newly diagnosed patients with SH.

Materials and methods

Seventy females participated in study. Among them there were 50 patients with SH, mean age 58.3 (± 8.53), and 20 controls without SH, mean age 51.1 (± 6.79).

We determined next parameters: TSH, FT₄, anti TPO-antibody (by ELISA method), and glycaemia, insulinemia, HgA1c, and performed oral glucose tolerance test to all who did not already have diabetes mellitus type 2.

We measured body weight, weight, and height. We calculated BMI and HOMA indexes. For statistical calculations we used EXCEL, Med-Calc and SPSS Programs.

Results

The patients were older then controls, they had higher levels of waist (W) and BMI. In the group of patients we found significantly higher percent of diabetes mellitus type 2 (DM2), 36%, and among them 14% newly diagnosed DM2. In the control group there were no DM. In the patients group, as expected, we found higher levels of TSH, anti TPO-Ab, and lower levels of FT₄. Concentration of glucose and HgA1c were higher among the patients. There were statistical significantly difference between the groups in waist F = 5.64, P = 0.020; glucose F = 4.40, P = 0.040; HgA1c F = 4.90, P = 0.030; TSH F = 116.62, P < 0.001; FT₄ F = 5.97, P = 0.017; and anti TPO-Ab F = 63.23, P < 0.001. We did not find statistical significance in HOMA and insulinemia. We found that there was positive correlation between the concentration of glucose and TSH (R = 0.304, P = 0.032) in patients group, but not in the control group. We did not find positive correlation between glucose and FT₄ in both groups.

Conclusions

Considering the results of our study we recommend determination of glucose levels (and, if necessary OGTT) in every patient whom we diagnosed SH.

DOI: 10.1530/endoabs.32.P1031

Coexistent toxic adenoma and Riedel thyroiditis: a case report

Abbas Ali Tam¹, Didem Ozdemir¹, Panmir Eren Ersoy², Aydan Kiliçarslan³, Reyhan Ersoy¹ & Bekir Çakıcı¹
¹The Department of Endocrinology and Metabolism Disorders, Atatürk Training and Research Hospital, Ankara, Turkey; ²The Department of General Surgery, Atatürk Training and Research Hospital, Ankara, Turkey; ³The Department of Pathology, Medical School, The Center for Health Practice and Research, Yıldırım Beyazit University, Ankara, Turkey.

Riedel thyroiditis is a rare chronic inflammatory disease of the thyroid. It is characterized by replacement of normal parenchyma with dense fibrotic tissue. Peripheral tissues might also be affected and this may cause airway obstruction, dysphagia, recurrent laryngeal nerve palsy and hypoparathyroidism. We report a patient with toxic adenoma previously treated with radioactive iodine and histopathologically confirmed Riedel thyroiditis.

Case

A 61 years old male patient was referred because of subclinical hyperthyroidism. He did not have any obstructive symptoms. In physical examination, a 20 x 20 cm nodule was detected in the left lobe. Serum TSH, FT₄, FT₃ and thyroglobulin levels were 0.047 μU/ml (0.4–4 μU/ml), 2.04 pg/ml (1.57–4.71 pg/ml), 1.03 ng/dl (0.85–1.78 ng/dl), and 6.31 mg/dl (1.15–35 mg/dl) respectively. Antithyroid peroxidase, antithyroglobulin and thyroid stimulating antibodies were negative. Thyroid ultrasonography revealed a 15 × 20 × 28 mm isoechogenic nodule located in superior and mid portions of left lobe. Ultrasonographically the nodule had a thin hypochlocotic halo, cystic degeneration areas and macrocalcification. Thyroid scintigraphy showed an active nodule with extranodular suppression of thyroid parenchyma. Uptake was 10% after 4 h and 25% after 24 h of ¹³¹I administration. The nodule was evaluated with fine needle aspiration biopsy and cytology was benign. The patient was treated with 20 mci radioactive iodine for toxic adenoma. In follow up, since nodule diameter increased significantly after 6 months, total thyroidectomy was performed. In histopathological examination, there was marked fibrosis in stroma and some atrophic glands in thyroid tissue. Fibrosis was extending to the surrounding fat tissue and focal chronic inflammatory cells...
were observed around middle sized veins. With these findings, the patient was diagnosed to have Riedel thyroiditis.

Conclusion

Riedel thyroiditis is a very rare disease of the thyroid gland. To our knowledge, this is the first case with coexistent toxic adenoma and Riedel thyroiditis reported in the literature.

DOI: 10.1530/endoabs.32.P1033

P1035

**The natural history of subclinical hyperthyroidism: a single centre experience**

Panagiota Anagnostis, Zoe Efthathiadou, Chrisanthis Zoulis, Albana Soukia, Athanasios Panagiotou, Eleni Karathanasi & Marina Kita

Department of Endocrinology, Hippokration Hospital of Thessaloniki, Thessaloniki, Greece.

Introduction

The possibility of progression of subclinical hyperthyroidism (SH) to overt hyperthyroidism (OH) is a critical point in deciding whether to treat this situation. The aim of this study is to evaluate the rate of progression of SH to OH and the factors influencing this outcome.

Methods/design

This is a retrospective study at an endocrine referral service in Northern Greece. Data from patients with SH diagnosed between 1996 and 2011 were extracted from the department’s electronic database. Patients with past history of thyrotoxicosis treated with radioiodine, surgery or antithyroids, thyroiditis, pregnancy/postpartum state, severe illness and pituitary disease were excluded.

Results

Forty patients (37 females/3 males) aged 53.9±14.3 years (range 25–76) were included. Mean TSH values at baseline were 0.19±0.13 mU/l. In 18 patients (45%) the diagnosis was subclinical Graves’ disease (GD), 13 (32.5%) multinodular toxic goitre (MTG) and 9 (22.5%) toxic adenoma (TA).

Progression to OH was seen in five patients, (12.5%), in two (11.1%) with GD, two (22%) with TA and one (7.7%) with MTG, during a mean follow-up time of 34.2±21.3 months. OH was observed in 4/56 (11.1%) at 1 year, 1/23 (4.5%) at 2 years, 0/15 (0%) at 3 years and 1/17 (5.9%) at 5 years. Three of five patients with SH progressed to OH in 6 months.

Interestingly, eight patients at 1 year (22%) normalized thyroid function, 5 (23%) at 2 years, 4 (27%) at 3 years and 6 (35%) at 5 years of follow-up. Five of seven (71.4%) with available follow-up data remained euthyroid during follow-up.

Conclusions

GD was the most common etiology of SH. A very small proportion of patients progressed to OH over 5 years. However, a considerable amount of patients with SH returned to normal thyroid function either for the remainder of follow-up, or only to return to SH state.

DOI: 10.1530/endoabs.32.P1035

P1034

**Comparison of pre- and post-levothyroxine hs-CRP and fetuin-A levels in subclinical hypothyroidism**

Mehmet Calan1, Oktay Bilgir2, Ferda Bilgir3, Ozlem Calan2 & Turker Cinali2

1Department of Endocrinology and Metabolism, Dokuz Eylul University Medical School, Izmir, Turkey; 2Department of Internal Medicine, Izmir Bozyaka Education and Research Hospital, Bozyaka, Izmir, Turkey; 3Department of Allergy and Immunology, Celal Bayar University Medical School, Manisa, Turkey.

Background

The objective of this trial is to determine pre- and post-levothyroxine treatment levels of inflammation markers, high sensitive-C reactive protein (hs-CRP) and fetuin A in cases with subclinical hypothyroidism.

Material and methods

A total of 32 patients with a diagnosis of subclinical hypothyroidism and a control group of 30 healthy individuals were tested for hs-CRP and fetuin A levels followed by administration of 50 μg levothyroxine in the patient group for 3 months. During post-treatment stage, hs-CRP and fetuin A levels in the patient group were re-assessed and compared with pre-treatment values.

Results

Pre-treatment levels of both hs-CRP and fetuin A were observed to be higher than the control group. The decrease in hs-CRP levels during post-treatment stage did not reach a statistically significant level (P: 0.440). However, decrease observed in post-treatment fetuin-A levels was found to be statistically significant (P: 0.012).

Conclusion

The decrease in fetuin A levels in subclinical hypothyroidism cases indicates that levothyroxine treatment exerts antiinflammatory and antiapoptotic actions. Even though the decrease in hs-CRP level is statistically insignificant, it is estimated to reach significant levels with sustained treatment.

Keywords

Subclinical hypothyroidism, hs-CRP, fetuin A, levothyroxine.

DOI: 10.1530/endoabs.32.P1034

P1036

**Morpho-functional features of rabbit’s thyroid gland with its autotransplantation in the thigh muscle**

Igor V Makarov, Tatyana A Fedorina, Larisa T Volova & Anastasia V Bodrova

Samara State Medical University, Samara, Russia.

The aim of our study was to determine the possibility of engraftment and function of the native thyroid tissue in its autotransplantation in the thigh muscle in rabbits. The experiment included 10 animals species Chinchilla Breed at the age of 12–18 months – five females and five males. In order to simulate the animals primary postoperative hypothyroidism animal extrafascial thyroidectomy was performed, and then on the inside of the left thigh of the neurovascular bundle formed femoral canal in the hip adductors, which fits within the thyroid tissue. Thyroid hormone levels before surgery was 1.0485 ±0.05 pg/ml for T₄ and 1.2082 ±0.05 pg/ml for T₃. During the first 3 weeks, showed a decline in hormone levels, reaching a minimum for 4th week – 0.8344 and 1.085 pg/ml for T₄ and T₃, respectively. Restoring the original hormone levels was observed in four rabbits, 2 months, in three rabbits – 3 months. Two rabbits were followed for 6 months after surgery, and thyroid hormone levels in 2 months remained above average, slightly decreasing after 3 months. In the early postoperative period (1 week) two rabbits
died of pulmonary complications, in the late postoperative period – one (uterine bleeding). The conclusion of the experiment was conducted according to international standards in the period of 3 months (five rabbits) and 6 months (two rabbits). Histological examination of material from the site of transplantation showed a massive proliferation of connective tissue and fat, increased vascularization of the muscles in the area of operation. However, the thyroid tissue not visualized either macroscopically or with standard staining with hematoxylin-eosin and picrofuchsin.

metaanalysis of data showed that the risk of recurrence if total thyroidectomy is performed. But not indicated for all patients.

P1037
Sexual dysfunction in women with thyroid pathology
Valea Ana, Ghevrava Cristina, Silaghi Alina, Iacob Iulia, Tomescu Florica, Terec Adina & Duncan Ileana
Endocrinology Department, University of Medicine and Pharmacy 'Iuliu Hatieganu', Cluj-Napoca, Romania.

Introduction
Sexual dysfunction is a particular pathology with relative high prevalence, often underestimated in general population. It’s manifest as an impairment of sexual desire, orgasm, sexual excitement or pain related to intercourse. Often sexual dysfunction is a result of systemic diseases or changes of sexual hormones. Thyroid pathologies, particularly hyper and hypothyroidism, with high frequency in women, causes problems with sexual performance related with changes of unbound sex hormone and individual response to organic disease. Materials and methods
We analyzed 20 women with hyperthyroidism and 30 women with hypothyroidism, admitted in Endocrinology Clinics of Cluj-Napoca. Through history were established menstrual cycle disorders and disorders of sexual function quality based on a questionnaire completed by each patient voluntarily. Also hormonal determinations were performed to examine thyroid and ovarian function.

Results
In the group with hyperthyroidism we obtained a frequency of 40% of sexual dysfunction. Regarding menstrual cycle disorders, there was a relatively uniform distribution, without significant quantitative changes between the group with amenorrhea, bradimemorrhia and polymenorrhea. In 20% of cases we reported no menstrual disorders.

In the hypothyroidism group we achieved a higher frequency of sexual disorders 53.3%, compared with the group with hyperthyroidism, with the same uniform distribution in terms of menstrual disorders. In 20% of cases with sexual dysfunction, the disorders of orgasm, arousal and sexual desire were reported only after the thyroid disease debut.

Conclusions
Sexual dysfunction is more common in women with hypothyroidism compared to those with hyperthyroidism. For both groups most affected disorders of sexual dysfunction were orgasm and sexual arousal. In hypothyroidism, low FT3 level and increased PRL influence sexual activity in women.

Menstrual cycle disorders are more common in the group with hypothyroidism, directly related to testosterone surge.

DOI: 10.1530/endoabs.32.P1037

P1038
Relationship of benign thyroid disorders with histological alterations of breast tissue. (Preliminary results of an observational study conducted in Greece)
Anna Angelousi1, Evangelia Zapanti2, Maria Prokopiou2, Grigoris Koutakis2 & Konstantinos Kontzoglou1
1Division of Endocrinology, University Hospital, Brabois, Nancy, France; 2Division of Endocrinology, Laiko General Hospital, Athens, Greece.

Introduction
The association of thyroid disorders including autoimmune thyroiditis with the risk for breast cancer is controversial (1–4). A recent study found that triiodothyronine (T3) levels are positively associated with breast cancer specific mortality (5). Experimental studies have shown that T3 mimics the effects of estrogen in human breast cell lines and induces the expression of progesterone receptors (6).

Purpose
The relationship of benign thyroid diseases (BTD) with histopathological alterations of breast tissue diagnosed by biopsy.

Methods
Ninety-three women were followed in an outpatient clinical center for breast diseases (23 premenopausal, 64 postmenopausal and 6 in perimenopausal period). Seventy of them were diagnosed for breast cancer (BC), 20 for benign breast disease (BBD) and 3 for atypia. The history of BTD was determined by medical records and personal interviews. Patients were divided into four groups based on their thyroid functional or morphological status (autoimmune hypothyroidism (10 patients), non autoimmune hypothyroidism (5 patients), hyperthyroidism of any cause (3 patients) and nontoxic goiter (15 patients)). Thyroid hormones functional tests and anti-TPO Ab titres were measured before any surgery or treatment (chemotherapy or radiotherapy).

Results
The overall prevalence of BTD was 22 in 70 (31.4%) women with BC and 8 in 20 women (4%) with BBD (P=0.592). No association to BC or BBD was found when studying each type of BTD separately (P=0.135). These results were independent to thyroid treatment (P=0.594). Mean FT3, FT4 and TSH concentrations in women without treatment for BTD, showed no difference between BC and BBD patients (P=0.249, P=0.187, P=0.209 respectively). FT3 levels were not associated to the concentration of estrogen or progesterone receptors of breast cancer cells (P=0.683). Anti-TPO Ab (>50 IU/ml) were not associated to specific histopathological patterns (P=0.641).

Conclusions
Preliminary data show that although overall prevalence of BTD is increased in BC patients compared to patients with BBD the difference was not statistically significant probably due to the small sample.

DOI: 10.1530/endoabs.32.P1038

P1039
Clinical outcomes in Graves' disease after therapy with anti-thyroid drugs, surgery, or radiiodine
Yamina Aribi1, Samia Ould kadibia1, Lila Brakni2, Lamia Hadjres3, Meriem Koli3, Samir Ait Abdrahamane1, Fatih Bentayeb1, Zoubir Sellai1, Meriem Bensaleh2, Zahra Kemali2, Reda Nacer Khodja2, Meriem Medjaher2 & E M Haffaf2
1Department of Endocrinology, Central Hospital of the Army, Algiers, Algeria; 2Department of Nuclear Medicine, Central Hospital of the Army, Algiers, Algeria.

The most common cause of hyperthyroidism in young patients is Graves’ disease (GD). It is an auto immune disorder caused by TSH-receptor-stimulating auto antibodies. Treatment options for GD include anti-thyroid drugs (ATD), radioactive iodine (RAI), and surgery. The treatment modalities used vary in different parts of the world.

Objectives
To compare the effect of different treatment and to determine the profile of patients who undergo such and such a treatment modalities outcome.

Methods
A retrospective study between 2007 and 2012 at the central hospital of the army. 100 GD patients were included and received different treatment.

Results
We treated 100 patients (63 men and 37 women) the average age was 33 years. 42 patients received ATD, 17 patients randomized to surgery, and 35 patients were treated with RAI. Subjects were followed for mean of 31 months (range, 1–69 months) for the following clinical outcomes: 73% of patients treated by ATD experienced persistent/recurrent hyperthyroidism. 100% of patients who underwent surgery became free of disease after total thyroidectomy without recurrence. Complication rate was 18%, 81% were successfully treated (hyperthyroid or euthyroid) after a single dose of RAI with no acute complication.

Conclusion
In our opinion the medical therapy (ATD: 24 months) is not a very performed therapy in our country taking into account our socioeconomic context. Thyroidectomy can be performed with low complication rates and there is no risk of recurrence if total thyroidectomy is performed. But not indicated for all patients. The RAI is a safe and effective treatment for GD. It is relatively inexpensive. For our young military patients it is the ideal therapy for a speedy recovery with no acute complication.

DOI: 10.1530/endoabs.32.P1039
P1040
Thyroid hormone elevates IL6 tissues content and causes hypoleptinemia
Carolina Biz, Lila Missae Oyama, Monica Marques Telles & Claudia Oller do Nascimento
Universidade Federal de São Paulo, São Paulo, São Paulo, Brazil.

Oxidative stress is regarded as a pathogenic factor in hyperthyroidism. IL6 has been described as acting as a protective intrahepatocellular against oxidative stress and mitochondrial dysfunction. On the opposite way leptin has been shown to increase oxidative stress. The impact of thyroid hormones on circulating cytokines levels has been demonstrated with conflicting results both in human and rats. Most of the studies concerned hyperthyroidism showed increased levels of IL6 compared either with controls. Our purpose was to determine the effect of hyperthyroidism and hypothyroidism on the concentration of IL6 in different tissues and leptin serum concentration. Male Wistar rats (60 days of age) were randomly distributed into three different groups: C – control group that received daily i.p. injection of vehicle; Hyper – hyperthyroid rats group that received daily i.p. injection of T4 (50 μg/rat); Hypo - hypothyroid rats group that received daily i.p. injection of propylthiouracil (50 μg/rat). 21 days after treatment, the animals were killed and serum, retroperitoneal adipose tissue, EDL and soleum muscles, and liver were collected. Tissues IL6 level, body weight gain, serum lipid profile, leptin and insulin were determined. The serum lipid profile and body weight gain and food consumption were similar among groups. All analysed parameters were similar between Hypo and C. However, the Hyper showed: increase in liver and EDL IL6 level; decrease in serum leptin levels; and elevation in insulin and glucose serum concentration. These results demonstrated that 21 days of propylthiouracil treatment did not affect the analysed parameters. However, the increase in tissues IL6 content and decrease leptin levels in T4 treated group could be a compensatory modulation of the oxidative stress caused by hyperthyroidism state.

DOI: 10.1530/endoabs.32.P1040

P1041
The determination of nitric oxide levels in treatment-naive hypothyroid females: pilot study
Zoran Gluvic1, Jelica Tica Jevtic1, Zorica Rasic-Milunovic1, Vesna Popovic-Radinovic1, Marina Vujovic1, Milena Lackovic1, Ivana Resanovic1, Esma R Isevin1, Marija Poplin-Taric1, Anita Vasic-Vlasavljevic1 & Nevena Paunovic1
1Zemun Clinical Hospital, Zemun, Serbia; 2Laboratory for Molecular Genetics and Radiobiology, Institute Vinca, University of Belgrade, Belgrade, Serbia; 3Railway Health Care Centre, Belgrade, Serbia.

Background
Hypothyroidism is an atherosclerosis-promoted condition. On the other hand, nitric oxide (NO) has antiatherogenic cardioprotective properties. By some Doppler ultrasound parameters (intima-media complex thickness (IMCT) and systolic velocity (SV)), one can point out the level of atherosclerosis presence in cardiovascular system out of histopathology. We primarily determine NO levels in studied population and then examine their influence on mentioned Doppler ultrasound parameters.

Methods and design
In this pilot study, 28 females were divided into hypothyroid and euthyroid-control group (15 and 13 participants, respectively). The NO levels were determined by using of ELISA test. All subjects were referred to one experienced ultrasonographist for measurement of IMCT (mm) and SV (ms) on right femoral artery. Obtained data were analysed by SPSS.

Results
Overall median NO levels at presentation were 37.00±29.28 and differed between groups (χ² = 47.000, P < 0.05). Registered median NO levels were 33.4 and 54.02 in hypothyroid and control group, respectively. An average overall IMCT and SV were 0.80 ± 0.18 mm and 0.52 ± 0.14 ms, respectively. Regarding to them, there were no statistical difference between groups (t Wilcoxon=1.821; χ² SV=77.500, P>0.05). NO levels neither correlated with TSH and IMCT (r pcorr=-0.256; ρ SVr=-0.283; P>0.05), nor influenced on IMCT and SV (r pcorr=-0.291; ρ SVr=-0.111; P>0.05).

Conclusion
This pilot study reveals higher NO levels in euthyroid group in comparison with treatment-naive hypothyroid females. Despite that the fact such difference is of statistical significance, small sample size and type of study are important limitations to generalize the conclusion. Additionally, there is registered no influence of NO levels on both Doppler ultrasound atherosclerosis markers. It is necessary to continue this study in regard to determine cut-off values of NO and to explain what in fact lower or higher NO levels mean in individual patient.

DOI: 10.1530/endoabs.32.P1041

P1042
Haemodialysis-induced changes in thyroid hormones and thyrotropin
Jiri Horacek1, Sylvie Dasilova-Sulkova2, Eva Malirova2, Blanka Dlabalova2, Roman Safranek2, Michaela Kubisova4, Marta Kalousova3, Jaroslav Maly2 & Pavel Zaky1
1Department of Internal Medicine IV, Faculty of Medicine and University Hospital in Hradec Kralove, Charles University in Prague, Hradec Kralove, Czech Republic; 2Faculty of Medicine and University Hospital in Hradec Kralove, Haemodialysis Centre, Charles University in Prague, Hradec Kralove, Czech Republic; 3Department of Nuclear Medicine, Faculty of Medicine and University Hospital in Hradec Kralove, Charles University in Prague, Hradec Kralove, Czech Republic; 4Department of Internal Medicine III, Faculty of Medicine and University Hospital in Hradec Kralove, Charles University in Prague, Hradec Kralove, Czech Republic; 5First Faculty of Medicine and General University Hospital in Prague, Institute of Clinical Chemistry and Laboratory Diagnostics, Charles University in Prague, Prague, Czech Republic.

Introduction
In end-stage renal disease (ESRD), thyroid function tests are often abnormal, and their interpretation is not always straightforward. While haemodialysis (HD) procedure has well-established profound effects on the serum levels of a variety of molecules no such data have been published on thyroid hormones.

Methods
In 110 ESRD patients, total and free thyroxine (T4m and fT4), total and free triiodothyronine (T3 and fT3), reverse triiodothyronine (rT3) and TSH levels were measured before and after a routine 4-h HD procedure using radioisotope assays.

Results
All thyroid hormones rose significantly (P<0.001, Wilcoxon) during HD: T4 by (median) 18.1% from (median) 70.9 to 91.1 nmol/l, T3 by 45.5% from 12.07 to 17.87 pmol/l, T3 by 14.6% from 0.98 to 1.12 nmol/l, rT3 by 8.7% from 3.39 to 3.61 pmol/l, and TSH by 15.7% from 0.265 to 0.311 nmol/l. Conversely, TSH levels after HD (median 1.60 mU/l) were significantly lower (P<0.001, Wilcoxon) than before HD (1.80 mU/l), probably reflecting the feedback inhibition.

Conclusion
The concordant rise in all thyroid hormones, with obvious maximum in T4m, together with a decrease in TSH, suggests an increased release of the hormones (preferentially of fT4) from the thyroid gland. This may be due to a removal of an inhibitor during HD procedure, perhaps of an excess of iodide (Wolff-Chaikoff effect), giving further support to the presumed link between iodine excess and increased prevalence of goitre and hypothyroidism in ESRD. Other putative inhibitors among non-specific uremic toxins may also be involved, as well as metabolic acidosis correction during HD. Finally, the information about timing of blood sample (before vs after HD) may be important for proper interpretation of thyroid function tests in HD patients.

DOI: 10.1530/endoabs.32.P1042

P1043
Simultaneous occurrence of hyperthyroid and hyperglycemic emergency in a middle aged woman
Eleni Armeni1,2 & George Karlis1
1Sismanoglio Hospital, Athens, Attiki, Greece; 22nd Department of Obstetrics and Gynecology, Aretaieio Hospital, National and Kapodistrian University of Athens, Athens, Attiki, Greece.

Introduction
Thyroid storm is a rare condition, reflecting an extreme physiological state within the spectrum of thyrotoxicosis. The disorder consists of the clinical manifestations of thyrotoxicosis in association with altered mental status. On the other hand, excess circulating thyroid hormones are associated with glycemic disorders, like hyperglycemia and insulinopenia. Moreover, diabetic ketoacidosis has been associated with thyroid storm in few cases. We report the case of a patient who developed hyperglycemic hyperosmolar state (HHS) and thyroid storm.

Case report
A 77-year-old woman with history of diabetes mellitus presented complaining for nausea, vomiting, dry cough and epigastric sensation for 3 days of duration. The...
clinical examination revealed slight disturbance of consciousness, 40
breaths/min, 140 bpm and temperature of 37.4 °C. The chest X-ray and the
urine sample were negative for infection, while the electrocardiogram showed
sinus tachycardia. Laboratory studies revealed random blood glucose levels
814 mg/dl and mild metabolic acidosis, compatible with HHS. Hyperglycemia
resolved rapidly after i.v. administration of normal saline and insulin, but the
clinical signs remained unaffected. Additionally, the patient developed acute
psychotic syndrome after 72 h. Laboratory data revealed thyrotoxicosis
(TSH=0.005 µU/ml, FT3=5.19 ng/dl), after which the patient admitted
previous noncompliance to the treatment. Thyroid storm was diagnosed at this
point, with a score of 70 points according to the thyroid storm score by Burch and
Wartofsky. The symptoms resolved after administration of thiamazole 60 mg and
atenolol 50 mg, daily.

Discussion
Thyroid storm should be diagnosed immediately using clinical criteria, in order to
improve outcomes. An upper respiratory tract infection was the apparently
precipitating factor, inducing the development of both HHS and thyroid storm.
However, a direct interaction between the two conditions cannot be ruled out,
especially due to their simultaneous occurrence.

DOI: 10.1530/endoabs.32.P1043

P1044
Immune associations in chronic thyrotoxicosis: December 2012
Catalina Poiana1, Marta Caruso1, Daniela Cristina Staicu1, Alexandra Clodeanu2 & Dan Pereteanu2
1CI. Parhon Institute of Endocrinology, Bucharest, Romania; 2Societatea Civila Medica Povernei, Bucharest, Romania.

Objectives
To investigate how the immune associations (IA) may have significance for
diagnosis or therapy in thyrotoxicosis.

Material and method
i) Patients: A. ‘Classical’ Hashimoto thyrotoxicosis (hyper-ATPO-emia, HT)=1196;
B. thyrotoxicosis with isolated hyper-ATG-emia, with normal ATPO (T-ATG)=73;
C. thyroids ‘séro-negative’ (normal ATPO and ATG, pathology diagnosis)=8;
D. idiopathic myxedema (hypothyroidism, no A, B, C)=69; E. Control=1130.
ii) Statistical analysis: χ2 test.

Results
i) Total IA: HT=220 (18.39%, P<0.001); T-ATG=20 (27.4%, P<0.001);
’séro-negative’=1 (12.5%, NS); idiopathic myxedema=9 (13.04%, NS); control=
107 (9.47%). ii) Main IA: A. Graves-Basedow disease: TH=155 (12.96%);
T-ATG: 5 (6.85%); B. Vitiligo: HT=36, P<0.0001; T-ATG=2, Control=10.
C. Dermatitis: HT=26, P<0.001. D. Immune ovariits with precocious
menopause: HT=16, P=0.004. E. Biermer anemia: HT=13; P<0.001.
F. Drug allergy: HT: 24, P<0.001. G. Rheumatoid arthritis: HT=8, but
in controls=19 (NS). H. Thrombophilia: HT=7, Control=1 (P=0.04).
I. Repetitive zona zoster: HT, Control=1 (P=0.04); Otosclerosis: HT=7,
Control=2 (P=13). iii) Multiple associations- very frequent (no 100):
exempts: Cerebral vasculitis with Sneddon sd, pulmonary fibrosis, cryoglobu-
linemia, virus C hepatitis (IEN), sicca sd; Sarcoidosis with drug allergy,
scleroderma, adenomagaly, arthritis; Asthma with postpartum trombophilia and
antiphospholipidic sd; Selective alopecia areata (no eyebrows), ferritine anemia,
miopata; Sharp disease, zona zoster, dispesia, alopecia areata, trombocytosis.

Conclusions
i) HT and T-ATG has immune associations with increased frequency.
ii) The most significant and prevalent association are: Graves-Basedow, vitiligo, Biermer
anemia, drug allergy, early menopause with immune ovariits, thrombophilia.
iii) HT, T-ATG and idiopathic mixedema are not significantly associated with
other immune conditions; rheumatoid arthritis, IDDM, B/C hepatitis. iv) Multiple
immune associations are common.

DOI: 10.1530/endoabs.32.P1045

P1045
Graves’ disease and cardiovascular risk factors
Carla Brandão1, Celestino Neves4,9, Carmo Palmares2, Oksana Šokhatska2, César Esteves1, Camila Dias6, Miguel Pereira1, Luís Delgado6, Davide Carvalho6 & José Luis Medina6
1Service of Endocrinology, Diabetes and Metabolism, São João Hospital Centre, Porto, Portugal; 2Department of Immunology, São João Hospital Centre, Porto, Portugal; 3Department of Health Information and Decision Sciences, Porto, Portugal; 4Faculty of Medicine, University of Porto, Porto, Portugal.

Objective
To evaluate the interrelationships between Graves’ disease (GD) and cardiovascular
risk factors.

Subjects and methods
We analyzed thyroid function tests, anti-thyroid antibodies, BMI, insulin resistance
markers, namely homeostasis model assessment for insulin resistance (HOMA-IR and HOMA-B), the quantitative insulin sensitivity check index (QUICKI), hepatic insulin sensitivity index (HISI), whole body insulin sensitivity index (WBISI), insulinogenic index (IGI) and the levels of total cholesterol (TC), LDL, HDL, LDL-cholesterol, triglycerides (TG), apolipoprotein B (ApoB), ApoA1, lipoprotein (a) (Lp[a]), homocysteine, C-reactive protein (CRP), folic acid and vitamin B12, in 108 subjects with GD (51 with overt hyperthyroidism and 55 with euthyroidism). A 75-g OGTT was performed and blood samples were obtained
every 30 min for 120 min for measurements of plasma glucose, insulin and
C-peptide levels. Statistical analysis was performed with Mann–Whitney and
Spearman’s correlation tests. Results are expressed as mean ±SD and odds ratio.
a two-tailed P<0.05 was considered significant.

Results
94% of studied subjects were female. Mean age and BMI were similar between
both groups. In hyperthyroid subjects, we found significantly higher levels of
TRAb (8.3±10.7 vs 2.3±4.8 IU/ml, P<0.001), CRP (0.84±1.55 vs
0.28±0.36 mg/dl, P=0.04), and significantly lower WBISI values (5.01±3.21 vs
6.73±4.23, P=0.02). In the total group, TSH levels were negatively correlated with HOMA-IR (r=-0.22; P<0.05), IGI (r=-0.31; P<0.01) and
TRAB levels (r=-0.46; P=0.02), FT3 and FT4 levels were positively correlated
with HOMA-IR (r=0.28, P<0.01 and r=0.26, P=0.02, respectively) and negatively correlated with WBISI (r=-0.23; P=0.03 and r=-0.26, P=0.02,
respectively). In the euthyroid group, TSH levels were positively correlated with
WBISI (r=0.29; P<0.05). In the hyperthyroid group, FT3, levels were negatively correlated with HSI (r=−0.38, P<0.02) and TSH and TRAB were negatively correlated (r=-0.32, P=0.02). Conclusions: The interrelationships between
thyroid function, insulin resistance and CRP translate an increased cardiovascular
risk in hyperthyroidism due to Graves’ disease.

DOI: 10.1530/endoabs.32.P1046
P1047
Clinical and subclinical hypothyroidism and their relation to cardiovascular risk factors
Ioana Golu, Mihaela Vlad, Mioara Cornianu, Dana Amzar & Cristina Tudoran
Department of Endocrinology, University of Medicine and Pharmacy ‘V Babes’, Timisoara, Romania; Department of Morphopathology, University of Medicine and Pharmacy, ‘V Babes’, Timisoara, Romania.

The cardiovascular system (CVS) is one of the major targets of thyroid hormone action. The thyroid function has a direct effect on heart rate, cardiac output and systemic vascular resistance. The prevalence of hypothyroidism in the general population is high, particularly in females (9−15%). Overt hypothyroidism is associated with severe cardiovascular manifestations including reduced intravascular volume, increased systemic vascular resistance (SVR), and reduced contractility and cardiac oxygen consumption. Clinical hypothyroidism is associated with premature atherosclerosis and increased prevalence of coronary disease. All manifestations are potentially reversible with thyroid hormone replacement.

We have studied 132 subjects with hypothyroidism admitted in Clinic of Endocrinology Timisoara in period 2011−2012, aged 20−87 years (52.47±12.23 years). They were divided by sex, age, living environment (urban, rural), value of cholesterol, heart rate, BMI, and blood pressure. Data on thyroid status, aortic atherosclerosis, and history of myocardial infarction were obtained at baseline. In the study group 89/132 patients had overt hypothyroidism and 43/132 subclinical hypothyroidism.

The study revealed an increased risk of cardiovascular abnormalities and an increased risk of atherosclerosis. Total cholesterol, triglycerides, and the systolic time intervals (increased SVR) were clearly elevated only in overt hypothyroidism. 27/89 cases with overt hypothyroidism had pericarditis.

The cardiovascular risk is associated with heart disease, but it is also influenced by the patient’s age as well as the severity and duration of hypothyroidism. Close monitoring of thyroid function could be the best option for patients at high risk of progression from subclinical to overt disease.

DOI: 10.1530/endoabs.32.P1047

P1048
The usefulness of thyroid function test in patients presenting with symptomatic bradycardia/complete heart block
Gideon Mlawa & Maria Silveira
Croydon University Hospital, London, UK; Winchester Hospital, Winchester, UK.

Background
The causes of symptomatic bradycardia/complete heart block are multifactorial. Bradycardia/complete heart block may be drug induced, electrolyte imbalance, ischaemic heart disease, or thyroid dysfunction. Hypothyroidism and electrolyte disturbances are reversible.

Objectives/aims
To identify/find out whether thyroid function test where performed in patients presenting with bradycardia/CHB in keeping with good practice before insertion of permanent pace maker (PPM).

Standards
i) thyroid function test done on admission-100%. ii) thyroid function test done out of hours-100%.

Methods
We collected data from a list of 54 patients who needed PPM insertion from electrophysiology department/cardiology for the past 3 months. This was a retrospective audit.

Results
Twenty patients (37%) had their thyroid function test prior to having PPM inserted, and 34 patients (67%) did not.

Conclusion
Hypothyroidism is reversible cause of symptomatic bradycardia/complete heart block and thyroid function test should done prior to insertion of permanent pace maker (PPM).

DOI: 10.1530/endoabs.32.P1048

P1049
Subacute thyroiditis: unusual presentation and diagnostic troubles
Rosa Maria Paragliola, Maria Pia Ricciato, Vincenzo Di Donna, Laura Castellino, Rosa Maria Lovicu, Alfredo Pontecorvi & Salvatore Maria Corsello
Catholic University School of Medicine, Rome, Italy.

A 73 years old man came to our observation for severe dysphagia and loss of weight (10 kg in 1 month). About 30 years before he had myocardial infarction and he underwent coronary artery bypass graft. One week before the first medical evaluation, patient suspended all drugs per os because he could not swallow pills and food. Thyroid function test revealed a severe hyperthyroidism (FT3 11.9 pg/ml; FT4 40 pg/ml; TSH <0.01 μU/ml). Anti-TSH receptor and anti-TPO autoantibodies were negative while thyroid ultrasound showed an increased gland with inhomogeneous pattern, without nodules or abnormal vascularization. He did not take amiodarone. He started methimazole 30 mg/day, without any benefit. Patient then came to our evaluation about 1 month after the onset of symptoms: clinical examination showed tachycardia, enlarged and tender thyroid gland at neck palpation without relevant pain. Biochemical evaluation showed increased VES and C-reactive protein. Thyroid scintigraphy was not performed because of the interference caused by iodine contrast medium (coronary angiography performed few days before). Nevertheless subacute thyroiditis appeared strongly probable. Therefore methimazole was stopped and steroid therapy was started with i.v. methylprednisolone 40 mg for 1 week, 20 mg for 1 week and then prednisone 25 mg/day, which was tapered and continued for 30 days. Clinical symptoms, and in particular dysphagia, improved after few days of i.v. methylprednisolone while biochemical evaluation performed after 2 months showed a normalization of thyroid function test and inflammatory parameters. In conclusion, we described an unusual case of subacute thyroiditis in which only dysphagia and thyrotoxicosis, without anterior neck pain, suggested an inflammatory condition. Diagnosis was made on the basis of clinical and laboratory features, because thyroid scintigraphy with RAIU, which is crucial for differential diagnosis in uncertain condition, was not possible to be performed for iodine overload.

DOI: 10.1530/endoabs.32.P1049

P1050
Simplified approach for the treatment of post-thyroidectomy hypocalcemia: a Pilot study
Punchangam Ramakanth Bhargav
Care Hospital, Khammam, India.

Introduction
One of the notable morbidity after total thyroidectomy is hypocalcemia related symptoms. Various treatments ranging from oral to parenteral calcium have been advocated. In this context, we analysed the benefits of bolus calcium vis-a-vis infusions for symptomatic post-thyroidectomy hypocalcemia.

Patient and methods
The study was conducted in Endocrine Surgery Department in a tertiary care hospital. All the patients with benign thyroid disease, who underwent total thyroidectomy and suffered from symptomatic hypocalcemia were included. The data was prospectively analyzed seperately for Group A treated with intermittent bolus calcium and Group B treated with decememntly graduated calcium infusion. All the patients were supplemented with equal doses of oral calcium and vitamin D.

Results
The study period was 12 months (October 2011−September 2012). Group A and B included 32 and 30 cases respectively. 7/90 in Group B and 1/32 in Group A suffered from thrombophlebitis. Treatment costed mean of INR 232 in Group A and INR 665 for Group B. Both thrombophlebitis and cost factors were statistically significant. Symptomatic hypocalcemia lasted for a mean of 2.3 days in Group A vs 2.5 days in Group B, which was statistically insignificant. None of the patients in both groups suffered from permanent hypoparathyroidism.

Conclusions
Intermittent bolus calcium treatment appears to be less expensive, simpler and less morbid approach compared to continuous infusion for treating post-thyroidectomy hypocalcemia.

Keywords
Hypocalcemia; Thyroidectomy; Thrombophlebitis, vitamin D, hypoparathyroidism.

DOI: 10.1530/endoabs.32.P1050
P1051

The influence of thyroid hormones on the variability of blood pressure
Tanja Nisic, Milos Stojanovic, Mirjana Stojkovic, Biljana Beleslin, Jasmina Ciric, Tijana Lalic, Bozo Trbovic & Milos Zarkovic
Clinic of Endocrinology, Belgrade, Serbia.

Introduction
Changes in thyroid function have significant impact on the cardiovascular system.

Methods
In a group of 37 subjects the level of thyroid hormones FT₄, FT₃, and TSH were measured. Then carried out short-term analysis for 30 min measuring variability of blood pressure with non-invasive TASK FORCE monitor. Registered data were analyzed by spectral analysis of variability. Statistical analysis were done by Pearson correlation model.

Results
The analysis of the parameters of the variability of systolic blood pressure (SBP), we confirmed that FT₄ positively correlated with parameters of spectral analysis of variability of systolic blood pressure: sBP LF; sBP LF/HF (p < 0.05), sBP LF, sBP PSD (p < 0.001). Discovered a negative correlation with sBP HF nu (p < 0.05) FT₁, is positively correlated with parameters of systolic blood pressure variability: sBP LF nu, sBP LF, sBP PSD, sBP LF/HF (< 0.05). TSH is positively correlated with sBP HF nu (r=0.4379) and HF SBP (p < 0.05).

The analysis of correlation with thyroid hormone parameters of diastolic blood pressure variability has been found for FT₁ – negatively correlated with DBP HFnu (p < 0.05) and positive correlation with DBP LF (p < 0.05).

Conclusion
Our study demonstrates a significant correlation between thyroid hormones and a systolic blood pressure and less important correlation with parameters of diastolic blood pressure variability. The analysis of variability of systolic blood pressure observed a positive correlation between FT₄ and FT₁ with parts of the spectrum of low frequency (sympathetic activity) and total spectral power (PSD). FT₁ and FT₃ were in negative correlation with parts of the spectrum of high frequency (parasympathetic). TSH correlated positively with the parasympathetic nervous system.

Analysis of variability of diastolic blood pressure registered a small number of significant correlations and FT₁ – negatively correlated with DBP HFnu (p < 0.05) and positive correlation with DBP LF (p < 0.05).

DOI: 10.1530/endoabs.32.P1051

P1052

Serum concentrations of cholesterol and triglyceride in patients with type 2 diabetes and incident hypothyroidism
Juan J Diez & Pedro Iglesias
Hospital Ramón y Cajal, Madrid, Spain.

Background
Subclinical thyroid hypofunction and elevation of serum lipid concentrations are two factors that may act synergistically in the increase of cardiovascular risk in patients with type 2 diabetes. However, the association between subclinical hypothyroidism and dyslipidemia is a matter of debate.

Objective
Our aim has been to assess whether incident hypothyroidism detected in a screening program is accompanied by elevations in the serum concentrations of cholesterol and triglyceride in a sample of patients with type 2 diabetes and no previously known dyslipidemia.

Patients and methods
From a total population of 1112 patients with type 2 diabetes who were screened for thyroid dysfunction (thyrotropin measurement) we selected a group of 325 patients with normal thyroid function and another group of 21 patients with incident hypothyroidism (20 of them with subclinical hypothyroidism). No patient had known dyslipidemia nor was taking hypolipidemic medication.

Results
Patients with incident hypothyroidism showed serum concentrations of total cholesterol (4.97 ± 0.73 mmol/l), HDL-cholesterol (1.36 ± 0.33 mmol/l), LDL-cholesterol (2.99 ± 0.57) and triglyceride (1.23 (0.89–1.53) mmol/l) that did not differ from those found in euthyroid patients (4.79 ± 0.83, 1.33 ± 0.36, 2.87 ± 0.76 and 1.11 (0.81–1.43) mmol/l, respectively). When analyzing subgroups of women and patients with obesity, we could not find significant differences in lipid profile in patients with hypothyroidism and normal thyroid function. Thyrotropin concentration did not show any correlation with lipid levels in patients with incident hypothyroidism, although we found a significant correlation between thyrotropin and triglyceride in euthyroid subjects (r = 0.165; P = 0.003).

Conclusion
Our results show that, in our population, there are no significant differences in the serum concentrations of cholesterol and triglyceride between diabetic patients with normal and reduced thyroid function.

DOI: 10.1530/endoabs.32.P1052

P1053

The characteristics of thyroid pathology in patients with parathyroid adenoma
Fulden Sarac, Sunru Savas & Fehmi Akcicek
Department of Geriatrics Medicine, Ege University Medical Faculty, Izmir, Turkey.

Introduction
Thyroid and parathyroid pathology may coexist; classicaly, this is described in multiple endocrine neoplasia. Other nonsyndromic scenarios result in pathologies of these endocrine organs coexisting. The aim of the investigation the characteristics of thyroid pathology in patients with parathyroid adenoma.

Subjects and method
The study population included 42 (26 patients age <60 years vs 16 patients age ≥60 years) patients with parathyroid adenoma. Clinical presentation, biochemical and radiological details were noted. Concomitant thyroid pathology by neck ultrasonography (US) in all patients.

Results
In patients with age ≥60, levels of PTH and calcium, TSH, free T₃, free T₄, autoantibody against thyroid peroxidase (TPOAb) and autoantibody against thyroglobulin (TgAb) were found to be 109.9±23.7 pg/ml, 11.4±1.1 mg/dl, 4.1±0.9 μIU/ml, 2.4±0.8 pg/ml, 0.91±0.01 ng/dl, 123.7±31.7 IU/ml and 57±10.3 IU/ml, respectively. Of the 16 patients, 15 (93.7%) had thyroid nodules. Among 12 patients with thyroid nodules, 1 (6.6%) had malignant thyroid tumor. And also, 7 patients (43.7%) had hashimato thyroiditis. In patients with age <60, levels of PTH and calcium, TSH, free T₃, free T₄, autoantibody against thyroid peroxidase (TPOAb) and autoantibody against thyroglobulin (TgAb) were measured 121.9±34.0 pg/ml, 12.3±2.0 mg/dl, 2.9±0.8 μIU/ml, 2.7±0.9 pg/ml, 1.1±0.1 ng/dl, 190.1±42.9 IU/ml and 76.8±12.1 IU/ml, respectively. Of the 26 patients, 19 (73.0%) had thyroid nodules. Among 19 patients with thyroid nodules, 2 (10.5%) had malignant thyroid tumor. And also, 12 patients (46.1%) had hashimato thyroiditis.

Conclusions
The study was demonstrated that the frequency of thyroidopathies were high in patients with parathyroid adenoma. And also, the frequency of thyroid nodules were higher in patients with age ≥60 years than thats of patients with age <60 years.

DOI: 10.1530/endoabs.32.P1053

P1054

Learning and development of thyroid FNA in a endocrine clinic
Jaime Lorenzo, Boente Ruth, Antón Youso & Manuel Sas
Hospital Povisa, Vigo, Spain.

Background
Development of thyroid ultrasound and FNA is more frequent to make it in a endocrine clinic, that means to make more diagnosis medical process and so to avoid more outpatients visits. But it’s necessary a specific treaning. We tried to evaluated our treaning.

Material and methods
After specific treaning in radiologic department, we have compared our results in two consecutive periods. The first one in the first year after treaning developing FNAs and the second period in the next 1½ year with FNAs. In the second period we used Bethesda system.

Results
In the first phase we made 102 FNAs with 25 (24.5%) non diagnostic and 77 (75.5%) diagnostic, results are exhibited. In the second phase, 220 FNAs were made and: 27 (12.27%) non diagnostic and 193 (87.73%) diagnostic. Specific FNAs results are exhibited too. (Bethesda system: bening: 166, atipic: 14, suspicio neo folicular and Hurthle: 16, suspicius of malignant: 6, medular: 1).

Conclusions
FNAs thecneque development after period learning is possible in a endocrine clinic with satisfactory results, similar to others published series. Its useful to
patient because less visits to hospital, more efficient in your clinic activity and cheaper medical process. Bethesda system make easier communication between clinics and pathologists.

DOI: 10.1530/endoabs.32.P1054

P1055

Does a normal thyroid ultrasound image always accompany normal thyroid functions test results?

Abbas Ali Tam1, Cafer Kayā3, Rifki Üçler1, Ahmet Dirikoc1, Reyhan Ersoy2 & Bekir Çakır2

1The Department of Endocrinology and Metabolism Disorders, Atatürk Training and Research Hospital, Ankara, Turkey; 2Department of Endocrinology and Metabolism Disorders, The Center for Health Practice and Research, Yıldırım Beyazıt University, Ankara, Turkey.

Introduction

Nowadays, ultrasonography (USG) is being used very commonly and indispensably for diagnosing thyroid diseases. Heterogeneous appearance of thyroid parenchyma is associated with positivity for thyroid autoantibodies and hypofunctioning of thyroid gland. On the other hand, it is not determined whether thyroid parenchyma appearing totally of normal ecogenity on USG is related to presence normal thyroid function tests or otherwise. The objective of our study was evaluate the relationship between normal thyroid USG appearance and thyroid function tests with thyroid autoantibodies.

Material and methods

The study was planned prospectively and 218 patients’ thyroid USG images and laboratory tests were evaluated. The participants were classified into two groups composed of the homogeneous/ normoecogenic and the heterogeneous group, according to thyroid parenchyma appearance on USG.

Findings

We acquired homogeneous images on 103 cases and heterogeneous images on 115 of the cases. TSH level, anti-Tg and anti-TPO titres and thyroid volume was found to be significantly higher in heterogeneous parenchyma group (P<0.001), 83 cases with normal USG images (80.5%) had normal TSH levels and 7 cases in this group had positive anti-Tg (9.4%) and 23 cases had positive anti-TPO (27.7%). Out of the heterogeneous parenchyma group composed of 115 cases; 46 patients (40%) had high TSH level and 9 of them (19.6%) had positive anti-Tg and 35 (76.1%) had positive anti-TPO. We observed no difference in between the groups in regards to FT3 and FT4 levels. Age and thyroid volume were determined to correlate significantly and positively (r=0.171, P<0.012).

Conclusions

The thyroid gland ‘normal’ appearing on USG imaging, possibly accompanies normal serum thyroid function tests and negativity for thyroid antibodies. According to our results, thyroid USG is a perfect device for predicting normal thyroid functions, which could probably avoid unnecessary future laboratory tests as well.

DOI: 10.1530/endoabs.32.P1055

P1056

The cholesterol and Lp(a) levels in Hashimato’s thyroiditis

Demet Özgil Yetkin1 & Betül Dogantekin2

1Icerenkoy Bayindir Hospital, Istanbul, Turkey; 2Goztepe Education and Research Hospital, Istanbul, Turkey.

Objective

The risk of atherosclerotic heart disease is increased in hypothyroidism. Although the reason is not clear. It is known that high level of Lp(a) is increases the risk of atherosclerotic heart diseases. The aim of this study is to investigate the relation between Lp(a) levels and thyroid hormones in the Hashimato’s patients.

Methods

One hundred and fifty Hashimato’s patient (50 patients diagnosed with clinic hypothyroid, 50 patients diagnosed with subclinic hypothyroid and 50 patients diagnosed with euthyroid) followed at Endocrinology outpatient clinic were enrolled in this study. The control group consisted of 50 age matched healthy volunteers. In every group, thyroid function tests (FT3, FT4, and TSH), lipid profile and Lp(a) levels were measured.

Results

The Lp(a) level at patients with clinic, subclinic and euthyroid Hashimato’s thyroiditis is higher than the Lp(a) level of control group (P=0.002; P<0.01). Total cholesterol and LDL levels were higher in all Hashimato groups than the control group (P=0.001; P<0.01). Triglycerid levels of patients in clinic hypothyroid group was higher than the control group (P=0.006; P<0.01). A significant relationship was found between Lp(a) levels and LDL levels in a positive manner (P=0.032; P<0.05) (r=0.152). There was a negative relationship between the TSH level and Lp(a) level at the group of euthyroid Hashimato’s thyroiditis.

Conclusion

The total cholesterol, LDL and Lp(a) levels were higher even in euthyroid Hashimato patients than the control group. This might have been the one of the reasons of increased atherosclerotic diseases in Hashimato’s thyroiditis.

Keywords

Hypothyroidism, Hashimoto’s thyroiditis, Lipoprotein(a), LDL cholesterol, total cholesterol, TSH.

DOI: 10.1530/endoabs.32.P1056

P1057

Comprehensive assessment of thyroid gland structure and function in men with metabolic syndrome

Oksana Tsygankova1, Elena Anufriienko2, Dmitry Platnov3, Julia Ekinova4 & Lyudmila Ruyatkina1

1Novosibirsk State Medical University, Novosibirsk, Russia; 2Research Centre for Clinical and Experimental Medicine of Siberian Branch of Russian Academy of Medical Sciences, Novosibirsk, Russia; 3Tver State Medical Academy, Tver, Russia; 4Institute of Therapy of Siberian Branch of Russian Academy of Medical Sciences, Novosibirsk, Russia.

Introduction

The aim of study was to perform a comprehensive structural and functional assessment of thyroid gland in men with metabolic syndrome (MS).

Methods

Main group (MG) of 116 men aged 35-60 years with MS (by International Diabetes Federation definition) and 34 healthy controls of the same age profile underwent a comprehensive examination of thyroid gland which included physical assessment, full serum thyroid hormonal profile – total and free triiodothyronine (T3) and thyroxine (T4), serum TSH, and high resolution ultrasonography. Conventional criteria for hyper- and hypothyroidism by thyroid hormonal levels were used; subclinical hypothyroidism was detected by elevated TSH with normal thyroid hormone levels.

Results

Thyroid volume was higher in MG than in controls (16.6 ±1.48 vs 10.1 ± 0.75, P<0.05), and overall structural abnormalities – much more frequent (in 71.6 vs 44.1%, P<0.05). Heterogeneous thyroid structures of all types with and without gland enlargement were seen in 19.0 and 42.2% in MG vs 8.8 and 35.3% in controls, whereas nodal changes (with size more than 1 cm) – only in MG (8.6%). Subclinical hypothyroidism was detected in 6 (5.2%) patients of MG, and in none of controls. However, in the rest of MG (cases of hypothyroidism excluded), mean TSH appeared to be lower than in controls (1.0 ± 0.19 vs 2.1 ± 0.24 mU/l, P<0.05), with free T4 being somewhat higher, albeit still within normal range (13.7 ± 0.69 vs 13.5 ± 0.63 pmol/l, P<0.05), and free T3 also normal and almost the same between groups. No manifested cases of hyper- or hypothyroidism were found in any group. Thus, contrary to structure, thyroid function was mostly normal in men with MS, and there was no clear association between structural and functional variables.

Conclusion

Structural abnormalities in thyroid gland are frequent in men with MS; usually they are not accompanied by significant hormonal dysfunction, and most hormonal alterations fall within normal range.

DOI: 10.1530/endoabs.32.P1057

P1058

Empirical calcium supplements paves way for day surgery complete thyroidectomy

Xina Lo, Tsz Kim Tam & Heng Tat Leong

North District Hospital, Hong Kong, Hong Kong.

Post operative hypocalcemia poses significant resistance to early discharge of total thyroidecтомised patients. Our institute implemented a new protocol to give empirical calcium and vitamin D supplements since Jan 2012 to prevent symptomatic hypocalcemia and facilitate early discharge. 75 (88.24%) out of 85 eligible cases did not have significant or symptomatic hypocalcemia and can be discharged by within 1 day with only two (2.67%) patients being readmitted electively for significant hypocalcemia on follow up. While in the selected
subgroup which excludes cancer cases, concomitant primary hyperparathyroidism and retrosternal goitres to be considered for day surgery, 58 (95.08%) out of 61 were able to be discharged on first post operative day without symptoms. All those who could not be discharged reported symptoms by at most 15 h. Within this group we had not excluded reoperation and controlled Graves’ disease cases, which previous series considered high risk with respect to day surgery and were excluded. Our results confirmed in well selected patient groups with routine calcium supplements and early follow up, discharging total thyroidectomised patients is feasible and safe within 24 h.

DOI: 10.1530/endoabs.32.P1058

P1059

Is TSH suppression an efficient thyroid nodular goitre therapy?

Karolína Drbalová1, MIroslav Vodák1, Monika Nývltová1, Inna Tučková1 & Martin Hůl1
1Central Military Hospital, Prague 6, Czech Republic; 2Institute of Endocrinology, Prague 1, Czech Republic.

Levotyroxine suppression therapy, i.e. keeping the TSH value below 0.5 mIU/L with the aim to reduce the total thyroid tissue or nodule volume, is an arguable and controversial issue not only due to the effect upon nodule volume but also because of the extent of necessary suppression, the effect of incomplete suppression, long-term therapeutic effects and risk of cardiovascular problems and osteoporosis.

The incidence of nodular alterations rises with age and in patients under the age of 20 show higher malignity risk. Fine needle aspiration biopsy (FNAB) is a safe and cost-efficient method of evaluating the biological character of nodules and choosing between a conservative and surgical treatment.

In our study, we investigated nodular alterations in patients under the age of 40, evaluated malignity presence by FNAB and observed the examined nodules in treated/untreated groups for at least 1 year. The objective was to set up the criteria that can predict nodular alterations in young patients and evaluate the benefit of suppression therapy.

The 3-year (2009–2011) prospective randomized study included 78 individuals, 65 of which accomplished observation: 32 treated and 33 untreated.

The treated/untreated variances were tested using ANOVA with repetition with the following factors: group, phase, subject and interaction, which evaluates variances in time.

Our results did not confirm statistically significant reduction of nodules in patients under the age of 40 subjected to 1-year suppression therapy compared to the untreated group. The input values of all patients before treatment showed statistically significant negative correlation between the nodules size and TSH value.

The conclusion of our study is that patients suffering from thyroid nodular alterations can be left untreated, upon FNAB evaluation, for minimum of 1 year.

Supported by MO CR 8310 Grant.

DOI: 10.1530/endoabs.32.P1059

P1061

Relationships between antithyroperoxidase antibody levels, thyroid function and echographic patterns in chronic thyroiditis: December 2012

Mara Carsote1, Catalina Poiana1, Daniela Cristina Stăicu2, Alexandrina Clodeanu2 & Dan Peretianu1
1C.I. Parhon Institute of Endocrinology, Bucharest, Romania; 2Societatea Civila Medica Povestiri, Bucharest, Romania.

Aim/objectives

To investigate relationships between thyroid function, antithyroperoxidase antibodies (ATPO), antithyroglobulin antibodies (ATG) and correlations with echographic pattern in Hashimoto thyroiditis and related diseases.

Materials and methods

Diagnosis: i) ATPO > 34 µIU/ml= Hashimoto thyroiditis (HT); ii) ATG =normal with high ATG= thyroiditis with only hyper-ATG (T-ATG). Thyroid function: TSH. Echographic patterns = 10 (Peretianu, this Congress). Statistical analysis: linear correlation, χ² tests.

Results


iii) TSH: a) onset HT: av: 8.83 µIU/l; b) onset T-ATG: 3.63 µIU/l; c) hypothyroidism HT: 41.12%; hypothyroidism T-ATG: 28.7% (χ² = 14.44, P = 0.044).

iv) Linear correlation ATPO/TH: a) in HT: HT at onset: r=0.00, P<0.001. All HT values: r=0.11, P=0.001; b) in T-ATG: HT at onset: r= 0.19, P<0.01 (NS). All T-ATG values: r = 0.17, NS.

v) Echographic pattern 8 in HT correlate with ATPO level (Table): χ²=24.9; P<0.001.

Table 1

<table>
<thead>
<tr>
<th>ATPO levels</th>
<th>Pattern 1 marked hypoechogenous pseudonodular</th>
<th>Pattern 8 only slightly hypoechogenous pseudonodular</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–34</td>
<td>21</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>34–100</td>
<td>180</td>
<td>12</td>
<td>192</td>
</tr>
<tr>
<td>100–350</td>
<td>324</td>
<td>39</td>
<td>363</td>
</tr>
<tr>
<td>350–999</td>
<td>336</td>
<td>25</td>
<td>361</td>
</tr>
<tr>
<td>1000–1999</td>
<td>244</td>
<td>10</td>
<td>254</td>
</tr>
<tr>
<td>2000–4999</td>
<td>73</td>
<td>1</td>
<td>74</td>
</tr>
<tr>
<td>&gt;5000</td>
<td>37</td>
<td>1</td>
<td>38</td>
</tr>
<tr>
<td>Total</td>
<td>1215</td>
<td>88</td>
<td>1897</td>
</tr>
</tbody>
</table>

Conclusion

i) A certain correlation exists between thyroid function but only for ATPO (not ATG), only in cohorts (not <400 probes), only in HT (not T-ATG): when ATPO increases, thyroid function decreases. ii) HT vs T-ATG evolve with more hypothyroidism. iii) Pattern 8 is related low ATPO levels as compared with pattern 1. Therefore, pattern 1 suggest more inflammation than pattern 8.

DOI: 10.1530/endoabs.32.P1061

Endocrine Abstracts (2013) Vol 32
Ten ultrasonographic thyroid pattern in Hashimoto’s thyroiditis: re-evaluation after 12 years
Dan Peretianu1, Catalina Poiana2, Mara Carsote1, Daniela Cristina Staicu1 & Alexandrina Clodeanu1
1Societatea Civila Medicala ‘Povereni’, Bucharest, Romania; 2C.I. Parhon Institute of Endocrinology, Bucharest, Romania.

Aim
To re-analyze the concept of echographic thyroid patterns (ETP) and clinical diagnostic in thyroidology, proposed 12 years ago.

Materials and methods
i) Between 1996 and 2012, > 25 000 thyroid ultrasound, linear probes, 7.5 MHz.


Patterns

<table>
<thead>
<tr>
<th></th>
<th>TH</th>
<th>T S-N</th>
<th>T-ATG</th>
<th>IM</th>
<th>GBD</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pattern 0</td>
<td>15</td>
<td>0</td>
<td>1</td>
<td>7</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Pattern 1</td>
<td>1223</td>
<td>1</td>
<td>57</td>
<td>17</td>
<td>9</td>
<td>84</td>
</tr>
<tr>
<td>Pattern 2</td>
<td>193</td>
<td>0</td>
<td>7</td>
<td>40</td>
<td>13</td>
<td>77</td>
</tr>
<tr>
<td>Pattern 3</td>
<td>74</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>138</td>
<td></td>
</tr>
<tr>
<td>Pattern 4</td>
<td>129</td>
<td>9</td>
<td>20</td>
<td>8</td>
<td>529</td>
<td></td>
</tr>
<tr>
<td>Pattern 5</td>
<td>205</td>
<td>0</td>
<td>8</td>
<td>1</td>
<td>20</td>
<td>39</td>
</tr>
<tr>
<td>Pattern 6</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>46</td>
</tr>
<tr>
<td>Pattern 7</td>
<td>74</td>
<td>0</td>
<td>5</td>
<td>11</td>
<td>13</td>
<td>261</td>
</tr>
<tr>
<td>Pattern 8 (new)</td>
<td>92</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>Pattern 9 (new)</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>1919</td>
<td>101</td>
<td>87</td>
<td>95</td>
<td>1183</td>
<td></td>
</tr>
</tbody>
</table>

Table 2

Sensitivity, specificity, and predictive positive value for the relationship pattern-diagnostic for HT vs all conditions.

Patterns

| Patterns in HT | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 (new) | 9 (new) |
|----------------|---|---|---|---|---|---|---|---|---|---------|---------|
| Sensitivity    | 0.78 | 63.73 | 10.06 | 3.86 | 6.72 | 10.68 | 0.31 | 3.86 | 4.79 | 0.21 |
| Specificity    | 98.57 | 88.61 | 81.19 | 89.26 | 61.05 | 94.07 | 96.86 | 80.22 | 98.50 | 99.86 |
| VPP            | 41.67 | 87.99 | 38.52 | 30.82 | 18.43 | 70.21 | 11.54 | 20.33 | 80.70 | 66.67 |
| VPN            | 80.70 | 66.67 | 43.13 | 74.51 | 42.80 | 41.22 | 30.25 | 46.79 | 42.13 | 36.93 |

Table 2

Conclusions
i) From sensitivity, specificity, and predictive positive value analysis, the classification proposed from 2003 in time (see Endocrine Abstracts 2007–2012) with only seven patterns ETP is exact and correct with ten ones, too: reliability: 84.7 and 93.97%. ii) VPP ~90 asks the diagnostic to be corroborated with antibody levels. Description ‘hypoechogenous-pseudonodular’ does not mean implicitly HT (could be T-ATG, too). iii) VPP >80% for pattern 4, means that, when there is a nodule over 10 mm, then HT is improbable. iv) When there are pattern 6 or 7, normality is almost sure. v) Patterns 1 and 8 suggest HT. vi) Patterns 5 and 9 suggest thyroiditis/Graves–Basedow with thyroid hyperfunction respectively euthyroidism.

DOI: 10.1530/endoabs.32.P1062

Superior vena cava syndrome due to enlarged thyroid gland
Evrim Cakir
Endocrinology and Metabolic Diseases Department, Amasya Sabuncuoglu Serefettin Training and Research Hospital, Amasya, Turkey.

Blood flow obstruction through superior vena cava leads to superior vena cava syndrome (VCSS). The most common cause of the VCSS is malignancies. Enlargement goitre is an unusual cause of VCSS. A patient with superior vena cava syndrome secondary to enlarged thyroid gland was presented in this case report. An 84-year-old man presented to endocrinology unit with gradually increasing neck mass, dysphagia, and shortness of breath. His physical examination revealed webbed neck with a marked thyroid swelling and multiple dilated tortuous veins with enlarged venous collaterals. An anterior posterior chest radiograph showed a widened superior mediastinum. The ultrasonography showed retrosternal goitre with heterogeneous parenchyma and nodules with cystic-necrotic degeneration. Neck computed tomography revealed heterogeneous, hypertrophic, nodular thyroid gland with multiple calcification and mediastinal extension with narrowed trachea. Thyroid function test was within normal limit. Enlargement goitres are easily recognised however, the initial presentation of superior vena cava syndrome due to subternal goitres with mediastinal extension is unusual.

DOI: 10.1530/endoabs.32.P1063

The change of character in passing of Graves’ disease in St Petersburg from 1970 to 2010
Svetlana Dora, Elena Krasilnikova, Anna Volkova & Evgenia Grigorieva
Saint-Petersburg Medical University named acad I.P. Pavlov, Saint-Petersburg, Russia.

The diseases of a thyroid gland belong to the most frequent pathology which is met among people. The prevalence and structure of pathology of a thyroid gland, first of all, depends from the level of a iodine status in the population. The first time the assessment of an iodine status in St Petersburg was carried out in 1999 by the staff of faculty therapy of Saint-Petersburg State Medical University named after academician I.P. Pavlov. The median urinary iodine concentration was 105 mkg/l. In 2010 the iodine status of St Petersburg was carried out again: the median urinary iodine concentration was significantly higher – 148 mkg/l.

This regard it was reasonable to carry a out comparison of indicators of an iodine status in St Petersburg and the features of a course of a Graves’ disease before the beginning of the actions for the elimination of iodine deficiency (till 1999) and during active iodine prophylaxis.

Materials and methods
There were 310 patients with a Graves’ disease, they were diagnosed during the period from 1970 to 2010.

Results
From 1980 to 2010 the number of remissions of the disease gradually decreased: till 1990 the number of remissions was 21.7% whereas from 2006 to 2011 the remissions were noted at 3.9% of patients with a Graves’ disease. The group of patients with disease recurrence was analysed separately. Till 1990 among the patients with recurrence of a disease developed in 207.00 – in 22.86 – 7.75 months, in the group 2001–2011 – in 28.59 ± 5.19 months, and in 2006–2011 – in 7.75 ± 1.21 months.

Conclusions
The carried-out research showed that for the last 20 years the essential change of character in the course of a Graves’ disease was noted. It is possible to suppose that the revealed features, most likely are connected with the change of the iodine status of the region.

Keywords
Graves’ disease, iodine deficiency, median urinary iodine concentration, iodine status.

DOI: 10.1530/endoabs.32.P1064
Subclinical autoimmune thyroid disease and cardiovascular risk factors

Cestelino Neves1,4, César Esteves1,4, Miguel Pereira3, Carmen Palmares2, Oksana Sokhatsha2, Camila Dias3, Luis Delgado1,2, Davide Carvalho1,4 & José Luís Medina1

1Service of Endocrinology, Diabetes and Metabolism, São João Hospital Centre, Porto, Portugal; 2Department of Immunology, São João Hospital Centre, Porto, Portugal; 3Faculty of Medicine, University of Porto, Porto, Portugal.

Objective
To examine whether Graves’ disease (GD) and autoimmune thyroiditis (AIT) are associated with insulin resistance and other cardiovascular risk factors.

Subjects and methods
We recorded thyroid function tests, BMI, insulin resistance markers comprising the homeostasis model assessment for insulin resistance (HOMA-IR and HOMA-B), the quantitative insulin sensitivity check index (QUICKI), hepatic insulin sensitivity index (HISI), whole-body insulin sensitivity index (WBISI), insulinogenic index (IGI) and the levels of total cholesterol (TC), HDL, LDL-cholesterol, triglycerides (TG), apolipoprotein B (ApoB), ApoA1, lipoprotein (a) (Lp(a)), homocysteine, CRP (C-reactive protein), folic acid and vitamin B12, in 83 patients with GD and subclinical hyperthyroidism (SCHyper), and in 83 patients with AIT and subclinical hypothyroidism (SCHypo). SCHypo was diagnosed based in the context of normal FT3 and FT4 levels. SCHyper was diagnosed based in the context of normal FT3 and FT4 levels.

We recorded thyroid function tests, BMI, insulin resistance markers comprising the homeostasis model assessment for insulin resistance (HOMA-IR and HOMA-B), the quantitative insulin sensitivity check index (QUICKI), hepatic insulin sensitivity index (HISI), whole-body insulin sensitivity index (WBISI), insulinogenic index (IGI) and the levels of total cholesterol (TC), HDL, LDL-cholesterol, triglycerides (TG), apolipoprotein B (ApoB), ApoA1, lipoprotein (a) (Lp(a)), homocysteine, CRP (C-reactive protein), folic acid and vitamin B12, in 83 patients with GD and subclinical hyperthyroidism (SCHyper), and in 83 patients with AIT and subclinical hypothyroidism (SCHypo). SCHypo was diagnosed based in the context of normal FT3 and FT4 levels. SCHyper was diagnosed based in the context of normal FT3 and FT4 levels.

Results
Ninety-five percent of studied subjects were female. In the GD group, TSH levels were negatively correlated with TRAb levels (r = −0.28; P = 0.04), and FT3 levels were positively correlated with HOMA-B (r = 0.40; P = 0.06). In this group, HOMA-IR and Lp(a) levels were positively correlated (r = 0.33; P = 0.02). In the AIT group, homocysteine levels were positively correlated with TSH levels (r = 0.27; P = 0.04), and negatively correlated with FT3 levels (r = −0.27; P = 0.04). In this group, BMI was negatively correlated with WBISI (r = −0.37; P = 0.004).

Conclusion
The interrelations between thyroid function, insulin resistance, homocysteine, Lp(a), and CRP levels translate an increased cardiovascular risk in subclinical autoimmune thyroid disease.

DOI: 10.1530/endoabs.32.P1066

Subclinical hypothyroidism, autoimmune thyroiditis, and cardiovascular risk factors

Teresa Pereira1, Cestelino Neves1,4, César Esteves1,4, Cláudia Camila Dias1, Miguel Pereira3, Oksana Sokhatsha1, Luis Delgado1,4, Davide Carvalho1,4 & José Luís Medina1

1Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar do Porto, Porto, Portugal; 2Faculty of Medicine, University of Porto, Porto, Portugal.

Objective
To evaluate the relationship between autoimmune thyroiditis (AIT), subclinical hypothyroidism (SCH) and cardiovascular risk factors.

Patients and methods
We recorded thyroid function tests, BMI, insulin resistance markers comprising the homeostasis model assessment for insulin resistance (HOMA-IR and HOMA-B), the quantitative insulin sensitivity check index (QUICKI), hepatic insulin sensitivity index (HISI), whole-body insulin sensitivity index (WBISI), insulinogenic index (IGI) and the levels of total cholesterol (TC), HDL, LDL-cholesterol, triglycerides (TG), apolipoprotein B (ApoB), ApoA1, lipoprotein (a) (Lp(a)), homocysteine, CRP (C-reactive protein), folic acid and vitamin B12.

Results
In this group, BMI was negatively correlated with WBISI (r = −0.37; P = 0.004). In the AIT group, BMI was negatively correlated with WBISI (r = −0.37; P = 0.004). In the group with SCH, FT3 correlated negatively with anti-TPO (r = −0.30; P = 0.04), and the levels of FT4 correlated negatively with anti-TPO (r = −0.28; P = 0.02).

Conclusions
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.32.P1067

Marine–lenhart syndrome

César Esteves1,4, Cestelino Neves1,4, Tiago Vieira3, Jorge Pereira3 & Davide Carvalho1,2

1Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar do Porto, Porto, Portugal; 2Department of Nuclear Medicine, Centro Hospitalar do Porto, Porto, Portugal.

Introduction
The Marine–Lenhart syndrome is a rare case of hyperthyroidism that is associated with the simultaneous or sequential presence of characteristics related to Graves’ disease and toxic nodular or multinodular goiter. Its validity as a disease is controversial and some authors believe that these are cases of hyperthyroidism where both etiologies coexist. The presence of hyperfunctioning nodules in Graves’ disease patients ranges between 0.8 and 4.3%.

Clinical case
We present three cases of Marine–Lenhart syndrome, all in female patients, aged 40–57 years old at the time of diagnosis. All cases had positive titers of anti-thyroid antibodies and thyrotropin receptor antibodies (TRAbs). The thyroid scans showed diffuse uptake with one or more hyperfunctioning nodules, without attenuation of the surrounding areas. One of the cases represents the occurrence of hyperthyroidism after treatment of toxic nodular goiter with radioactive iodine.

Discussion
The described cases present criteria for the diagnosis of Marine–Lenhart syndrome. Graves’ disease is more frequent in younger individuals, while Marine–Lenhart syndrome occurs in older ones, as occurs in Plummer’s disease. As these are cases that tend to recur, total thyroidectomy is the treatment of choice.

Conclusions
Marine–Lenhart syndrome is a controversial cause of hyperthyroidism. The importance of its diagnosis resides in the preference for surgical treatment.

DOI: 10.1530/endoabs.32.P1067
P1068
Is Hashimoto’s thyroiditis in children different from adults? A prospective comparative study
Panchangam Ramakanth Bhargav
Care Hospital, Khammam, India.

Background
Hashimoto’s thyroiditis (HT) is the commonest cause of spontaneous hypothyroidism. We compared clinico-investigative profile between child HT vs adult HT.

Material and methods
The study was conducted in Endocrine surgery department in a tertiary care hospital. The data was analyzed seperately for Group A: child HT (below 18 years) and Group B: adult (above 30 years).

Results
The study period was 30 months (October 2009–March 2012) with minimum follow-up of 10 months. Subjects included 95 child HT and 85 adult HT cases. 22/85 (26%) adult HT cases, required thyroidectomy for dominant nodule, pressure symptoms, etc. Cervical lymphadenopathy, diffuse goiter, painful thyroiditis rates were higher in children. Hypothyroidism in 26% of Group A compared to 4% in Group B was self-limiting.

Conclusions
Significant differences in the clinical profile and natural history between child HT and adult HT seems to distinguish them as separate entities.

Keywords
Hashimoto’s thyroiditis; Goiter; Hypothyroidism; Thyroidectomy.
DOI: 10.1530/endoabs.32.P1068

P1069
Evolution of thyroid function in Hashimoto thyroiditis and related disorders: December 2012
Catalina Poiana1, Mara Carsote1, Daniela Cristina Staicu2, Alexandrina Cloceanu* & Dan Peretianu2
1C.I. Parhon Institute of Endocrinology, Bucharest, Romania; 2Societatea Civila Medica Poverei, Bucharest, Romania.

Aim
Analyzing the evolution of thyroid function in thyroiditis and related disease during 1–17 years.

Materials and methods
i) Diagnostic: Hashimoto’s thyroiditis (HT): a) anti-thyperoxydase antibodies (ATPO) cut-off = 34 IU/ml. b) If ATPO = normal, thyroiditis was considered if high antithyroglobulin antibodies (T-ATG), c) Idiopathic mixedema (IM): hypothyroidism, no ATPO, no ATG, and no TRAB. ii) Patients: HT: 1196; T-ATG: 73; IM: 69. Women/men: HT: 1136/60; T-ATG: 69/4; IM: 60/9 (more men: 

Results
i) At the diagnostic moment. a) HT: euthyroid (EUT): 534 (44.5%), hypothyroid (HIT): 498 (41.5%), hyperthyroid (HIT): 168 (14%) – from these: 155 (~87%) associated with Graves–Basedow disease (GBD)–(TRAB Z 29%), HIT: 9 (12.3%) – from these: 5 (~55%) associated with GBD–(TRAB Z 2.76, S.D. 0.01). Despite levothyroxine withdrawal, she maintained a stable thyroid function under levothyroxine. Nevertheless, considering the prevalence of both condition, the first option seemed most likely. Patients with thyroid function fluctuation should be closely monitored. doi: 10.1530/endoabs.32.P1071

P1070
Abstract unavailable.
DOI: 10.1530/endoabs.32.P1070

P1071
Autoimmune hypo to hyperthyroidism: a rare evolution
Mafalda Marcelino, João Silva, Dolores Passos & João Jácome de Castro
Armed Forces University Hospital, Lisbon, Portugal.

Introduction
Hashimoto thyroiditis (HT; with anti-thyroid peroxidase antibodies (TPOAb)) and Graves’ disease (GD; with TSH receptor antibodies (TRAbs)) are frequent autoimmune disorders responsible for thyroid dysfunction. There are two types of TRAbs, the ones that stimulate the thyroid (TSAb) causing Graves’ hyperthyroidism and those that block thyrotropin action (TBAb) being occasionally responsible for hypothyroidism. Unusual patients switch from TSAb to TBAb (or vice versa) with concomitant thyroid function changes. The progression from a HT to GD is not frequent and there are only a few cases described in the literature.

Case report
A 63-year-old woman with history of obesity and depressive syndrome was referred to our department in 2006 due to increasing weigh, with a BMI 39 kg/m2. Neck ultrasonography (US) revealed thyroid nodules and the laboratory confirmed a HT (TPOAA +) with normal thyroid function. After 1 year follow-up, the patient presented with subclinical hypothyroidism (TSH 11.0), initiating treatment with levothyroxine 50 mg/day. Fine needle aspiration biopsy (FNAB) of thyroid nodule was benign. During 4 years, the patient maintained a stable thyroid function under levothyroxine. A five years after diagnosised of hypothyroidism, the patient presented a subclinical hyperthyroidism (TSH = 0.01). Despite levothyroxine withdrawal, she maintained hyperthyroidism complaints, with weight loss, palpitations, tremor and heat intolerance, initiating treatment with methimazol and β-blockers. After scintigraphy and TRAbs titration, the diagnosis of GD was confirmed.

Discussion
The distinction between an evolution from HT to GD or from TBAb to TSAb is very difficult. Although the presence of TPOAb suggested HT diagnosis, the concomitant presence of these antibodies with TRAbs is also frequent. Nevertheless, considering the prevalence of both condition, the first option seemed most likely. Patients with thyroid function fluctuation should be closely monitored.

Case report
A 39-year-old woman previously cured of mild thyroid autoimmune hypothyroidism noticed an enlargement and pain in the thyroid area after a probable viral infection with symptoms of increased body temperature. At the same time she developed a small lump on the superior edge of her thyroid cartilage. A few days later she noted a haematoma on her anterior neck and also noticed that the lump had disappeared. Sonographical examination confirmed thyroid enlargement with a nonspecific structural pattern and a 0.3 ml hypoechogenic spherical formation in place of the previously described lump. The haematoma was causal from the formation. No biopsy of the formation was performed due to its size and superficial placement of the formation.
Conclusion
The source of bleeding was not detected with certainty. We hypothesized that a rupture of a previously asymptomatic thyroglossal cyst occurred during subtotal (de Quervain’s) thyroiditis because of the sudden enlargement of both the thyroid and the cyst. Less probable is enlargement of the thyroid due to activation of pre-existing autoimmune thyroiditis.

DOI: 10.1530/endoabs.32.P1072

P1073
Acute respiratory failure in a rapidly-enlarging benign cervical goiter
Carlo Jan Garingarao1, Cecille Anonuevo-Cruz1 & Ryan Gasacao1,2
1Section of Endocrinology, Diabetes and Metabolism, University of the Philippines, Philippine General Hospital, Manila, The Philippines; 2Department of Otorhinolaryngology, University of the Philippines, Philippine General Hospital, Manila, The Philippines.

Benign goitres have the potential to reach massive sizes if neglected, but most have a protracted course that may or may not present with compressive symptoms. We report the case of a 57-year-old male who presented with a rapidly enlarging nodular goitre resulting in acute respiratory failure. Endotracheal intubation and emergency total thyroidectomy were done, revealing massive thyroid nodules with minimal intrathoracic extension and tracheal erosion. Despite a course and clinical findings suggestive of malignant disease, histopathology was consistent with a benign multinodular goitre. Several cases of benign goitres necessitating endotracheal intubation have been reported. Airway compromise was attributed to a significant intrathoracic component, or inciting events such as thyroid hemorrhage, pregnancy, radiodine uptake or major surgery; none of which were present in our case. Obstructive symptoms may not correlate well with objective measures of upper airway obstruction such as radiographs or flow volume loops.

DOI: 10.1530/endoabs.32.P1073

P1074
Vitiligo anti-thyroid peroxidase antibody
Chiriac Anca1, Foia Liliana2, Chiriac E. Anca2, Miron Claudia2, Solovan Caius1, Birsan Cristina1, Moscalu Mihaela2 & Stanciu Roxana1
1Nicolina Medical Center, Iasi, Romania; 2University of Medicine ‘Gr T Popa’, Iasi, Romania; 3University of Medicine ‘V Babes’, Timisoara, Romania; 4Individual Endocrinology Center Dr Miron Claudia, Iasi, Romania.

Vitiligo is a common skin depigmenting disease, which is thought to have, at least partly, an autoimmune etiology. Our objective was to compare the frequency of thyroid peroxidase antibody (anti-TPO) in vitiligo patients over a period of 3 years (2010–2012) in our Department. Methods

Anti-TPO levels were assessed in order to detect any correlation with the onset, the evolution and the treatment of vitiligo. Patients with vitiligo and with known thyroid disease, history of thyroid surgery and those receiving thyroid medications were not included.

Conclusions
According to our study, high levels of anti-TPO were shown to be more common in vitiligo patients, especially in young women. As this antibody is a relatively sensitive and specific marker of autoimmune thyroid disorders and considering the fact that vitiligo usually precedes the onset of thyroid dysfunction, periodic follow-up of vitiligo patients for detecting thyroid disease, is further emphasized especially in young women with increased level of anti-TPO.

As vitiligo usually appears before the development of the thyroid disease, it may be advantageous to screen thyroid functions and antibody levels in all patients with vitiligo – this is the observation addressed to the dermatologists. A patient diagnosed with autoimmune thyroiditis by the endocrinologist must be referred to a dermatologist in order to discover the first lesions of vitiligo, especially in the pediatric field.

DOI: 10.1530/endoabs.32.P1074

P1075
Protective antioxidative effects of caffeic acid phenethyl ester in the thyroid and the liver are similar to those caused by melatonin
Agnieszka Kokoszko-Bielska1, Jan Štepníak1, Andrzej Lewinski2,3 & Małgorzata Karbowik-Lewinska2,3
1Department of Oncological Endocrinology, Medical University of Lodz, Lodz, Poland; 2Department of Endocrinology and Metabolic Diseases, Medical University of Lodz, Lodz, Poland; 3Department of Endocrinology and Metabolic Diseases, Polish Mother’s Memorial Hospital – Research Institute, Lodz, Poland.

Whereas oxidative reactions occur in all tissues and organs, the thyroid gland constitutes such an organ, in which oxidative processes are indispensable for physiological functions. Thus, with additional oxidative abuse caused by several factors, increased oxidative damage to macromolecules may occur in the thyroid. In turn, numerous metabolic reactions occurring in the liver create favourable conditions for huge oxidative stress. Melatonin is a well-known antioxidant and free radical scavenger, with protective effects against oxidative damage perfectly documented in many tissues, the thyroid and the liver included.

Caffeic acid phenethyl ester (CAPE), a component of honeybee propolis, has been suggested to be also an effective antioxidant. It is even used as a protective agent during chemotherapy and radiotherapy regimens. The aim of the study was to evaluate the effects of CAPE on experimentally-induced oxidative damage in porcine thyroid and liver homogenates, and to compare the results with protective effects of melatonin.

Fenton reaction (Fe2+ + H2O2 → Fe3+ + OH− + OH− ) substrates were used to induce oxidative damage to membrane lipids (lipid peroxidation, LPO). Then, tissue homogenates were incubated in the presence of either CAPE or melatonin (0.1–500 µM) and, additionally, in the presence of Fenton reaction substrates. Whereas CAPE decreased basal LPO in a concentration-dependent manner in both tissues, melatonin did not change the basal LPO level. When antioxidants were used together with Fenton reaction substrates, they prevented – in concentration dependent manner and to a similar extent – experimentally-induced LPO in both the thyroid and the liver.

Protective antioxidative effects of CAPE in the thyroid and the liver are similar to those caused by melatonin. CAPE constitutes a promising agent in terms of its application in experimental and, possibly, clinical studies.

DOI: 10.1530/endoabs.32.P1075

P1076
Use of scintigraphy in the current diagnosis of thyroid diseases
Monika Nyvítova, Miroslav Vodák, Karolína Drbalová & Miroslav Zavoral
Military University Hospital Prague, Prague, Czech Republic.

Introduction
Scintigraphy had long been the only modality for thyroid gland imaging. With the development of other imaging techniques (sonography, CT, MRI), the role of scintigraphy has gradually diminished. However, it cannot be completely ignored, as it is the only technique to image not only the morphological structure, but also the functional status of the thyroid gland. In the current clinical practice, thyroid scintigraphy is performed with 99mTc pertechnetate, 131I (123I) at selected facilities and 99mTc MIBI in some indications. Possible uses of scintigraphy
i) Toxic goiter, independent adenoma, multinodular goiter (Figs 1–5).

ii) Functional residues of the thyroid gland after surgery (Figs 6–9).

iii) Ectopic thyroid gland.

iv) Thyroid nodules.

v) Thyroid scintigraphy.

Irreplaceable in patients after thyroid gland surgery due to thyroid cancer for visualization of thyroid gland residues and distant metastases (Figs 14–16).

vi) Differential diagnosis of subacute deQuervain’s thyroiditis with toxic syndrome (blockage of the accumulation of radiopharmaceuticals) and immunogenic hyperthyroidism (increased accumulation). (Figs 17–19).

vii) Parathyroid adenoma (Figs 20–22).

Conclusion
Thyroid scintigraphy has an irreplaceable role in the confirmation of thyroid residues after total thyroidectomy (carcinoma, Graves’ hyperthyroidism with orbitopathy) and localization of parathyroid adenomas. It is an elegant method for differential diagnosis of the thyrotoxic syndrome in patients with subacute thyroiditis and Graves’ disease. It provides a complementary technique for...
Thyroid cancer

**P1077**

**Association acromegaly and thyroid cancer**

Samia Achir, Fella Hassellouani, Anissa Khalifa & Mourad Semrouni
Department of Endocrinology and Nuclear Medicine, Algiers, Algeria.

**Introduction**

Acromegaly is a chronic disease caused by hypersecretion of GH and IGF1, it is associated with a high risk of cancer, however the excess incidence of thyroid cancer remains controversial, we report four cases.

**Patients and methods**

The diagnosis of acromegaly has been placed on a dosage of GH and IGF1, the diagnostic of carcinoma is based on histological study of the surgical specimen.

**Results**

The sex 9 predominant (3/4). For three patients (no. 1, no. 2, no. 4) thyroid carcinoma was the mode of revelation of acromegaly. Thyroid hormone function was normal in three quarters of cases. It was a GMN or a united nodular. The FNA made in 50% of cases was contributive in 100%. Papillary form (3/4).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Gender</th>
<th>TSH</th>
<th>FT4</th>
<th>TCT</th>
<th>Cytopuncture</th>
<th>Histological type</th>
<th>GH/IGF1</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. 1</td>
<td>2</td>
<td>34</td>
<td>HTG</td>
<td>NIE</td>
<td>NIE</td>
<td>NIE</td>
<td>Papillary</td>
<td>vascular</td>
<td>&gt;50 ng/l per NF</td>
</tr>
<tr>
<td>No. 2</td>
<td>2</td>
<td>59</td>
<td>GMN</td>
<td>NIE</td>
<td>NIE</td>
<td>NIE</td>
<td>Papillary</td>
<td>vascular</td>
<td>0-40 mui/ml</td>
</tr>
<tr>
<td>No. 3</td>
<td>2</td>
<td>51</td>
<td>GMN</td>
<td>NIE</td>
<td>NIE</td>
<td>NIE</td>
<td>Papillary</td>
<td>mesenchymoma</td>
<td>210 ng/l</td>
</tr>
<tr>
<td>No. 4</td>
<td>2</td>
<td>45</td>
<td>HT</td>
<td>NIE</td>
<td>NIE</td>
<td>NIE</td>
<td>Papillary</td>
<td></td>
<td>1168 ng/l</td>
</tr>
</tbody>
</table>

**Conclusion**

Despite the controversial results regarding the increased risk of thyroid cancer during the acromegaly, the exploring of thyroid is unavoidable and surgery must always be indicated when cytopuncture suspicious or malignant.

**P1078**

**Double primary carcinoma – a case of coexisting papillary thyroid carcinoma and pulmonary adenocarcinoma**

Jerome Barrera & Gabriel Jaul
Philippine General Hospital, Manila, Metro Manila, The Philippines.

A 49 year-old Filipino male presented at the emergency room because of progressive dyspnea. He was diagnosed with papillary thyroid carcinoma by fine needle aspiration biopsy of his 7×5 cm thyroid mass 3 months prior to his current consultation. He was scheduled to undergo total thyroidectomy but he opted to postpone his surgery due to intermittent cough. On admission, a pulmonary mass with pleural effusion on the right was noted on chest radiograph. He was considered to have papillary thyroid carcinoma with pulmonary metastases and malignant effusion. Ultrasound guided biopsy of the 3×5.8×5.3 cm pulmonary mass and cytologic studies of pleural fluid, however, revealed adenocarcinoma compatible with primary lung malignancy. Chest tube thoracostomy with JP drainage was done which resulted to improvement of the dyspnea. Plan was to do pleurodesis and chemotherapy of the more aggressive malignancy, the pulmonary adenocarcinoma, then total thyroidectomy, radioactive iodine ablation and thyroxine suppression therapy of the papillary thyroid carcinoma. However, patient developed sudden dyspnea and expired from pulmonary embolism.

The coexistence of two primary carcinoma – pulmonary adenocarcinoma and papillary thyroid carcinoma is a rare event. The relationship between these two cancers is still unclear. Management should focus on the more aggressive carcinoma first. In this case, it is the pulmonary adenocarcinoma since the latter carcinoma is known for its indolent course and better prognosis than the former.

**P1079**

**Rac1B: a prognostic marker for papillary thyroid carcinoma?**

Ana Luísa Silva1, Francisca Carmo1, Teresa Pereira1, Rafael Adame Cabrera2 & Maria João Bugalho1,2

**Introduction**

Identification of molecular markers with a reliable prognostic value may greatly improve the management of patients with papillary thyroid carcinoma (PTC). Rac1b, a hyperactive splice variant of the small GTPase Rac1, was found to be overexpressed in colorectal, breast and lung cancer. It has been shown to sustain tumor cell survival in colorectal cancer and was reported to have a key role in the malignant progression of breast and lung tumors. The Rac1b tumorigenic properties led us to investigate whether Rac1b was expressed in PTCs.

**Patients and methods**

The expression of Rac1b at transcript level was analyzed in a total of 61 PTC patients (mean age 41 years; F:M ratio 43:19) by qRT-PCR. In 23 cases, tumor and the corresponding normal paired sample were compared. Rac1b expression at protein level was confirmed by western blot and immunohistochemistry in selected representative cases. Patients were divided into two groups based on longitudinal analysis and final outcome (mean follow-up 6 years): group I included patients that underwent full sustained remission after initial treatment or presented stable residual biochemical disease; group II included patients with persistence of disease after primary treatment, patients with at least one relapse and those who died from disease.

**Results**

Rac1b expression in thyroid tissue was clearly detected at both transcript and protein levels. Moreover, we observed that Rac1b was overexpressed in 46% of PTCs and found a striking correlation between poor clinical outcome and Rac1b overexpression (P=0.0029).

**Conclusions**

Present results document expression of Rac1b in normal thyroid cells as well as overexpression in a subset of PTCs. Whether Rac1b actively participates in thyroid tumorigenesis will require further investigation. Also, future studies are needed to validate its use as a prognosis marker.

**P1080**

**A single-center, open-label, phase II, proof-of-concept study with pasireotide long-acting release in patients with progressive medullary thyroid cancer: 6-month evaluation**

Antongiulio Faggiano1,2, Piero Ferolla3, Giovanni Vitale3,4, Michela Del Prete1, Valeria Rumundo1, Raffaella Esposito, Vincenzo Marotta1, Francesca Marciello1, Anna Chiara Carratù1, Luigi Camera1, Rosi Fonti1 & Annamaria Colao1
1Department of Molecular and Clinical Endocrinology and Oncology, Federico II University of Naples, Napoli, Italy; 2Endocrinology, National Cancer Institute, “Fondazione G. Pascale”, Napoli, Italy; 3Department of Internal Medicine, University of Perugia, Perugia, Italy; 4Ospedale San Luca IRCCS, Istituto Auxologico Italiano, Milano, Italy; 3Department of Medical Sciences, University of Milan, Milano, Italy; 4Department of Biomorphological and Functional Sciences, Federico II University of Naples, Napoli, Italy.

**Introduction**

Medullary thyroid cancer (MTC) is a well-differentiated neuroendocrine tumor in which somatostatin receptor (sst) expression is higher for sst1 and sst5 than for sst2. This may explain why the available sst2-selective analogues do not work in MTC. Pasireotide LAR, a somatostatin analogue with high-binding affinity for sst1,2,3 and sst5 could be effective.

**Aim**

To evaluate the effectiveness of pasireotide long-acting release (LAR) in MTC patients with progressive disease.

**Study design**

Trial enrollment started in February 2012 (study registration no. NCT01625520). Twenty patients are expected to be enrolled. At now, 14 consecutive patients with progressive metastatic or persistent postoperative MTC have been enrolled and received pasireotide LAR 60 mg/m.
Introduction

Papillary thyroid carcinoma (PTC) is the most common endocrine malignancy, with a steadily increasing incidence in the last few decades worldwide. Studies revealed the predisposition to PTC by the heterogeneous state of rs2910164 within the precursor of microRNA146a. Interestingly, on the same chromosome, 40kb separate the pre-miR-146a from the pituitary tumour transforming gene (PTTG1), a proto-oncogene involved in thyroid carcinomas. A genome-wide study revealed an association of the genomic region encompassing pre-miR-146a and PTTG1 gene with systemic lupus erythematosus. In this study, we analyzed, with a case–control design, the genetic association between PTC and pre-miR-146a.

Methods

Two hundred and six healthy controls (30–78 of age) and 307 PTC patients (30–74 of age) were enrolled. The diagnosis of PTC was histological at surgery. Thyroid sonography was performed in controls to exclude nodules. SNP genotyping of pre-miR-146a and PTTG1 was performed by Sanger sequencing and high resolution melting. Linkage disequilibrium (LD) analysis and statistics were performed with Haploviev 4.2 and GraphPad Prism5 software.

Results and conclusions

Pre-miR-146a rs2910164 allelic frequencies were not statistically different in patients (C = 24.3%) and controls (C = 28.6%) and the SNP was not in LD with the investigated PTTG1 SNPs. We did not confirm a previous described association of the CG genotype with PTC. However, a significant association between the GG genotype and PTC (GG vs GC + CC odds ratio = 1.38, 95% CI 0.8–2.4) was found. The PTTG1 SNPs (rs1862391AAC and rs291021CCT), in perfect LD, have the same allelic frequency in patients (A = 76.7%) and controls (A = 76.2%) and are not associated with PTC. In conclusion, the study showed a new evidence of association between pre-miR-146a rs2910164 and PTC while PTTG1 did not seem to be involved.

DOI: 10.1530/endoabs.32.P1083

P1082

Association of pre-miR-146a rs2910164 GG genotype with papillary thyroid cancer: a new case–control study on two adjacent genes on chromosome 5, pre-miR-146a and PTTG1

Marco Marino1, Valentina Cirillo2, Valentina Gnarini1, Elisa Pignati1, Livio Casarin1, Chiara Diazza1, Vincenzo Rochira1, Katia Cioni1, Bruno Mased1, Manuela Simon1 & Laura Fugazza1

1Unit and Chair of Endocrinology and Metabolism, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Azienda AUSL of Modena-NOCSAE of Baggiovara, Via Giardi, Modena, Italy; 2Department of Medical Sciences, University of Modena, Endocrine Units Padiglione Granelli, Istituto di Ricovero e Cura a Carattere Scientifico Ca’ Granda, Via Francesco Sforza, 35, 20122 Milano, Italy.

DOI: 10.1530/endoabs.32.P1082

P1081

A novel multi-target pyrazolopyrimidine derivative with anti-neoplastic properties, CLM29, is active against medullary thyroid cancer in vitro and in vivo

Poupak Fallahi, Silvia Martina Ferrari, Guido Bocci, Concettina La Motta, Ilaria Ruffilli, Andrea Di Domenicantonio, Alda Corrado, Caterina Mancusi, Romano Danesi, Federico Da Settimo, Paolo Miccoli & Alessandro Antonelli

University of Pisa, Pisa, Italy.

Introduction

CLM29, a pyrazolo[3,4-d]pyrimidine compound, inhibits several targets (including the RET tyrosine kinase, epidermal growth factor receptor, vascular endothelial growth factor receptor and has an anti-angiogenic effect). Recently it has been shown to inhibit proliferation and migration in primary papillary differentiated thyroid cancer cells. The aim of this study is to evaluate the anti-tumor activity of CLM29 in medullary thyroid cancer (MTC).

Methods/design

The CLM29 anti-proliferative and proapoptotic effects (5, 10, 30, 50 µmol/l) were tested in vitro in primary MTC (P-MTC) cells obtained at surgery, in TT cells harboring (C634W) RET mutation, and in human dermal microvascular endothelial cells (HMVEC-d). TT cells were injected in CD mnu mice which were treated with CLM29.

Results

CLM29 (10 µmol/l, 30 µmol/l or 50 µmol/l) inhibited significantly (P < 0.001) the proliferation of P-MTC, or TT cells. CLM29 increased the percentage of apoptotic cells in TT and P-MTC cells dose-dependently (P < 0.001), while had no effect on migration and invasion. CLM29 inhibited significantly the proliferation, blocking extracellular regulated kinase 1 and 2 phosphorylation and inducing apoptosis in HMVEC-d. The inhibition of proliferation by CLM29 was similar in P-MTC cells with/without RET mutation. TT cells were injected s.c. in CD mnu mice and tumor masses became detectable between 20 and 30 days after xenotransplantation. CLM29 (50 mg/kg per die) inhibited significantly tumor growth and weight and the therapeutic effect was significant from the 40th day after cell implantation (18 days after the beginning of treatment). A significant reduction of Ki-67 immunostaining and of microvesSEL density was observed in the CLM29-treated tumors.

Conclusion

The anti-tumor activity of a ‘pyrazolo[3,4-d]pyrimidine’ compound, CLM29, has been shown in MTC in vitro, and in vivo, opening the way to a future clinical evaluation.

DOI: 10.1530/endoabs.32.P1081
Results
Patients with 12 month remission of disease had more frequently previous history of autoimmunity (P=0.008). Men had less frequently remission at t/fo and more frequently CA compared to women (26.3% vs 44.3%, 19.3% vs 8.6%, P=0.004).

P1084
Inhibition of proliferation in anaplastic thyroid cell lines
Joana Rodrigues1, Angela Rodriguez2, Sihara Perez3, Francisco Barreiro3, Jose Cameselle-Teijeiro1, Maria Rodriguez1, Susana Bravo1 & Clara Alvarez1
1Physiology, IDIS-CIMUS, School of Medicine, University of Santiago de Compostela, Santiago de Compostela, Spain; 2Surgery, IDIS-Hospital Clinico Universitario, University of Santiago de Compostela, Santiago de Compostela, Spain; 3Pathology, IDIS-Hospital Clinico Universitario, University of Santiago de Compostela, Santiago de Compostela, Spain.

Introduction
Our group has a bank of human primary thyroid cultures (BANTTIC) obtained from patients. All are individual cultures specifically genotyped and phenotyped. We believe of great interest the search for biomarkers in these cultures using differential proteomic analysis. We have applied differential proteomics using 2D-PAGE coupled to MALDI-TOF-TOF-MS. We have compared benign pathologies (normal thyroid and Pendred’s syndrome) and differentiated thyroid carcinomas (thyroid papillary carcinoma).

Individual protein quantities were evaluated by the Student’s t-test within the PDQuest analysis in order to compare the two groups and identify sets of proteins that showed a statistically significant difference with a confidence level of 0.05. One of the differential spots we have found (spot 8002) is increased in carcinoma cultures (T-PC) vs benign pathologies. Aim: To perform functional studies to investigate 8002 protein in anaplastic thyroid carcinoma cell lines.

Results
8002 protein is a low molecular weight variant with two isoforms. The gene encoding spot-8002 is related with nuclear functions but also it is described to bind to cytoskeleton.

Using western blot with specific antibodies for 8002 protein, experiments that compare primary thyroid cultures from BANTTIC and commercial cell lines, have showed that 8002 protein is processed and increased in Differentiated Thyroid carcinomas (DTC) and Anaplastic Thyroid Carcinoma (ATC) in comparison with Normal Thyroid (NT).

A specific 8002 siRNA was designed. When transfected in Papillary Thyroid Carcinoma, Follicular Thyroid Carcinoma and Anaplastic Thyroid Carcinoma cell lines has blocked proliferation of Anaplastic cell lines during several days. More functional studies will be carried out to investigate this protein.

DOI: 10.1530/endoabs.32.P1084

P1085
Pre-existing autoimmune thyroid disease may influence the course of the disease in differentiated thyroid carcinoma patients
Anastasia Athanasiadou1, Katerina Saltiki1,2, Gianna Rentziou1, George Papageorgiou1, Eleni Anastasiou1 & Maria Alevizaki1,2
1Endocrine Unit, Department of Medical Therapeutics, Alexandra Hospital, Athens University School of Medicine, Athens, Greece; 2Department of Endocrinology and Metabolism, Evangelion Hospital, Athens University School of Medicine, Athens, Greece.

Introduction
Differeniatated thyroid carcinoma (DTC) has generally a good prognosis and is associated with prolonged survival. A minority of patients may have persistent disease and rarely aggravation during t/fo. We investigated factors which may influence the persistence of disease in patients who had undergone ablative surgery with 131I.

Patients and methods
903 DTC patients were referred in our center from 1968 to 2012. Five hundred and forty-one (22.4% males) underwent thyroid remnant ablation and were followed-up for 1–44 years (7.9±4.3 years). Of those 344 (65.6%) showed remission during the 12 month Tg-stimulation test (Tg ≤ 1.0 ng/ml). Most of those who showed disease persistence (Tg > 1.0 ng/ml) underwent repeated treatments (>1 surgery and/or repeat 131I administration), while 39.1% finally showed remission (Group 1). Those with disease persistence were further divided in three subgroups according to stimulated Tg during t/fo: Group 2: low-Tg (≤ 5 ng/ml, no clinical aggravation (CA), n=47, 23.9%); Group 3: high-Tg (> 5 ng/ml, no CA, n=50, 25.4%) and Group 4: CA-group (n=23, 11.7%).

Endocrine Abstracts (2013) Vol 32

P1086
Evaluation of treatment approaches to thyroid hormone autoimmunity and hereditary medullary thyroid carcinoma in Turkey
Bagdagül Yüksel1, Benip Yilmaz2, Abdullah Taslipinar3, Alptekin Gürsoy4, Mazhar Müslüm Tuna5, Mehtap Vardar Basaran6, Ayşen Akkurt7, M Edo Ertörer8, Kadriye Aydin6, Sibel Güldiken9, Yasin Simsek10, Züleyha Karaca11, Merve Yilmaz12, Mijide Akkurt13, Inan Anaforgülu14, Nur Kebapçi12, Abdullah Taslipinar13, Mustafa Kulaksızoğlu6, Dilek Berker1, Tomris Erbas5 & Murat Fuik Erdogan1
1Department of Endocrinology and Metabolism Diseases, Faculty of Medicine, Ankara University, Ankara, Turkey; 2Department of Endocrinology and Metabolism Diseases, Ankara Numune Education and Research Hospital, Ankara, Turkey; 3Department of Endocrinology and Metabolism Diseases, Faculty of Medicine, Uludag University, Bursa, Turkey; 4Adana Department of Endocrinology and Metabolism Diseases, Faculty of Medicine, Baskent University, Adana, Turkey; 5Department of Endocrinology and Metabolism Diseases, Faculty of Medicine, Hacettepe University, Ankara, Turkey; 6Department of Endocrinology and Metabolism Diseases, Faculty of Medicine, Trakya University, Edirne, Turkey; 7Department of Endocrinology and Metabolism Diseases, Faculty of Medicine, Erciyes University, Kayseri, Turkey; 8Department of Endocrinology and Metabolism Diseases, Faculty of Medicine, Dokuz Eylül University, İzmir, Turkey; 9Department of Endocrinology and Metabolism Diseases, Faculty of Medicine, Gazi University, Ankara, Turkey; 10Trabzon Numune Education and Research Hospital, Trabzon, Turkey; 11Department of Endocrinology and Metabolism Diseases, Faculty of Medicine, Eskişehir Osmangazi University, Eskişehir, Turkey; 12Department of Endocrinology and Metabolism Diseases, Gülhane Military Medical Academy, Ankara, Turkey; 13Department of Endocrinology and Metabolism Diseases, Faculty of Medicine, Necmettin Erbakan University, Konya, Turkey.

Introduction
RET mutation analysis has a critical importance for determining clinical approach to hereditary medullary thyroid carcinoma (MTC). The current guidelines recommend to determine the timing of prophylactic thyroidectomy depending on the risk stratification, mainly decided by the type of the mutation.

Methods
Society of Endocrinology and Metabolism of Turkey (SEMT) sponsored ret genetic screening between July 2008 and January 2012 in 513 patients. Application forms of 513 patients whose blood samples were sent by their doctors to SEMT were assessed. We aimed to evaluate 319 eligible patients who had sporadic, familial MTC, MEN 2 or mutation carriers from known families. Physicians were asked to give information about, surgical history, latest calcitonin levels, survival of the patients and also further genetic screening and prophylactic thyroidectomies among family members. An evaluation form had been prepared for each patient and sent to their doctors all around the country. Twenty-five centers responded by filling in the forms of 192 patients.

Results
Mean follow-up period was 40 months. At the time of diagnosis 15 (13%) patients had stage 4 disease and 13 (86.6%) of these cases were sporadic. In their last follow up 80 patients (41.9%) had been prepared for each patient and sent to their doctors all around the country. Twenty-five centers responded by filling in the forms of 192 patients.

Mean follow-up period was 40 months. At the time of diagnosis 15 (13%) patients had stage 4 disease and 13 (86.6%) of these cases were sporadic. In their last follow up 80 patients (41.9%) had been prepared for each patient and sent to their doctors all around the country. Twenty-five centers responded by filling in the forms of 192 patients.

Endocrine Abstracts (2013) Vol 32
Malignancy. Micro-RNAs (miRNAs) are a new class of small, noncoding RNAs whose expression is deregulated in many types of human cancers and may lend novel clues to FTC genesis. Pre-miR146a represents one of the most up-regulated miRNAs in papillary thyroid carcinomas (PTC) and a SNP (rs2910164), identified in pre-miR146a, contributes to genetic predisposition to PTC, but data on FTC are still lacking. The objective of the study was to evaluate the expression of pre-miR146a in FTC both in neoplastic and non-neoplastic tissues that in relation to the rs2910164 SNP of pre-miR146a.

Results
Pre-miR146a expression levels were detected in 35 male and female patients with FTC, aged 53 ±18. RNA was extracted from surgically removed thyroid neoplastic and non-neoplastic FFPE samples. Total RNA containing miRNAs was used for stem-loop RT reactions. A standard TaqMan PCR kit protocol was implemented for real-time PCR. Reactions were performed on the CFX96 Real-Time System (Bio-Rad) with U6 RNA as an endogenous loading control. The pre-miR146a common G/C polymorphism, designated rs2910164, was genotyped by sequencing. Wilcoxon signed-rank test and Friedman test were used for statistical analysis.

Discussion
The expression of pre-miR146a is significantly down regulated in tumor compared to non-neoplastic tissues in patients with FTC (P = 0.043). rs2910164 genotype is related neither to the level of expression of pre-miR146a nor to the type of tissue analyzed. Finally, no correlations between the expression of pre-miR146a and the genotype of the SNP in the transition from non-neoplastic to neoplastic tissue in patients with FTC were found.

Conclusions
The expression of pre-miR146a is related to FTC but not to the rs2910164 SNP.

DOI: 10.1530/endoabs.32.P1089

P1087
Sentinel lymph node biopsy in thyroid carcinoma and decision for selective modified radical neck dissection
Radan Dzodic, Ivan Markovic, Igor Djurisic, Marko Buta, Marko Jevric, Merima Oruci, Zorka Inic, Zorka Milovanovic & Gordana Pupic
Institute for Oncology and Radiology of Serbia, Belgrade, Serbia.

Background
The accuracy of sentinel lymph node biopsy (SLNB) in decisions for surgical management of lymph nodes in thyroid carcinoma (TC) was demonstrated in a few previous studies. SLNB was started in good selected cases of medullary thyroid carcinoma (MTC) and it is a promising method. Its application to avoid prophylactic neck dissection is still lacking. The objective of the study was to evaluate the expression of pre-miR146a, in FTC both in neoplastic and non-neoplastic tissues that in relation to the rs2910164 SNP of pre-miR146a.

Aim
To determine whether SLNB of first draining node/s in jugulo-carotid chain is an accurate technique to select patients with true positive LN for selective modified radical neck dissection (MRND).

Patients and methods
We have performed SLNB in 172 patients with papillary TC and 12 cases with FTC. Before mobilization of the thyroid gland, 0.2 ml of 1% solution of methylene blue dye was injected peritumorally. After 10 min the dissection was continued around omohyoid muscle, towards the internal jugular vein and carotid artery until blue stained LN were found and sent for frozen-section examination. An extended dissection of level III/IV was done consecutively. All LN were examined by frozen section and conventional (HE) histopathology examination. If positive, MRND was performed after total thyroidectomy and routine dissection of central neck compartment.

Results
Identification rate of SLN was 94.5%. Specificity and sensitivity of the method were 99.3 and 84.4% respectively. Negative and positive predictive values were 96.5 and 96.4%. Overall accuracy of the method was 96.5%.

Conclusions
According to previous data, status of lower jugulo-carotid LN significantly predicts the status in upper two thirds. Our results imply that SLNB in the jugulo-carotid chain using methylene blue dye mapping, is feasible and accurate method for estimating LN status in the lateral neck compartment. The method may support a decision to perform selective MRND in patients with TC. Also it is a promising method for MTC in clinical N0 stage.

DOI: 10.1530/endoabs.32.P1087

P1088
Pre-miR146a expression profiling of follicular thyroid carcinoma
Elisa Pignatti1, Eleonora Vighi1, Luca Roncati2, Elda Karla1,4, Eleonora Porcheddu3, Elisa Magnani1, Vincenzo Rochira1,4, Merima Oruci3, Zorka Inic, Zorka Milovanovic & Gordana Pupic
Department of Diagnostic Medicine, Biomedical, Metabolic and Neural Sciences, University of Modena & Reggio Emilia, Modena, Italy; 2Department of Diagnostic Medicine, Clinical and Public Health, University of Modena & Reggio Emilia, Modena, Italy; 3Endocrinology and Metabolism, Geriatrics, Azienda USL of Modena, NOCSAE of Baggiovara, Modena, Italy.

Introduction
Follicular thyroid carcinomas (FTC) are the second most common type of thyroid malignancy. Micro-RNAs (miRNAs) are a new class of small, noncoding RNAs whose expression is deregulated in many types of human cancers and may lend novel clues to FTC genesis. Pre-miR146a represents one of the most up-regulated miRNAs in papillary thyroid carcinomas (PTC) and a SNP (rs2910164), identified in pre-miR146a, contributes to genetic predisposition to PTC, but data on FTC are still lacking. The objective of the study was to evaluate the expression of pre-miR146a in FTC both in neoplastic and non-neoplastic tissues that in relation to the rs2910164 SNP of pre-miR146a.

Results
Pre-miR146a expression levels were detected in 35 male and female patients with FTC, aged 53 ±18. RNA was extracted from surgically removed thyroid neoplastic and non-neoplastic FFPE samples. Total RNA containing miRNAs was used for stem-loop RT reactions. A standard TaqMan PCR kit protocol was implemented for real-time PCR. Reactions were performed on the CFX96 Real-Time System (Bio-Rad) with U6 RNA as an endogenous loading control. The pre-miR146a common G/C polymorphism, designated rs2910164, was genotyped by sequencing. Wilcoxon signed-rank test and Friedman test were used for statistical analysis.

Discussion
The expression of pre-miR146a is significantly down regulated in tumor compared to non-neoplastic tissues in patients with FTC (P = 0.043). rs2910164 genotype is related neither to the level of expression of pre-miR146a nor to the type of tissue analyzed. Finally, no correlations between the expression of pre-miR146a and the genotype of the SNP in the transition from non-neoplastic to neoplastic tissue in patients with FTC were found.

Conclusions
The expression of pre-miR146a is related to FTC but not to the rs2910164 SNP.

DOI: 10.1530/endoabs.32.P1089

P1089
68Ga-DOTA-NOC PET/CT role in the follow-up of patients with medullary thyroid carcinoma
Joana Couto1, Raquel Martins1, Inês Lucena1, Joana Menezes2, Ana Paula Santos1, Elisabete Rodrigues2, Hugo Duarte3 & Isabel Torres1
1Portuguese Institute of Oncology, Porto, Portugal; 2Centro Hospitalar de São João, Porto, Portugal.

Introduction
About 50% of patients with medullary thyroid carcinoma (MTC) have persistent or recurrent disease after surgery. For a calcitonin (ct) value greater than 150 pg/ml, it is suggested by international guidelines performing additional imaging exams (AIE) for evaluating the presence of distant metastases and secondary liver lesions (often miliary) by ‘morphological’ imaging (MI).

Objectives
To evaluate the role of 68Ga-DOTANOC PET/CT in the detection of residual disease or recurrence/metastatic lesions in patients with biochemically evidence of recurrence or persistence of MTC.

Methods
Retrospective study of patients diagnosed with MTC who underwent surgery and performed 68Ga-DOTANOC PET/CT at our institution between August 2010 and March 2012.

Results
Twenty-three patients, 16 (69.6%) females, aged between 26 and 78 years (median 54). 68Ga-DOTANOC PET/CT was performed from 4 months to 21 years, after the initial diagnosis of MTC (median 5 years). The main reasons for the exam’s request were high ct and/or no evidence of disease in conventional AIE and to evaluate the extent of the disease. In 65.2% of cases, ct value was >150 pg/ml. The exam revealed lesions in 12 cases (52.2%) and all of these had ct values >150 pg/dl. Among 12 patients with previous negative MI, 68Ga-DOTANOC PET/CT showed evidence of disease in five cases (42%). It provided additional information to MI in four cases.

Conclusions
In our series, 68Ga-DOTANOC PET/CT provided additional information in about 39% of cases. These results support the important role that 68Ga-DOTANOC PET/CT may have in the follow-up of MTC patients, particularly those with significantly high ct values. It could even select potential candidates for PRRT therapy.

DOI: 10.1530/endoabs.32.P1089

Endocrine Abstracts (2013) Vol 32
P1090

Distribution of ret proto-oncogene mutations among Turkish familial medullary thyroid cancer/multiple endocrine neoplasia 2 patients

Bagdagül Yüksel1, Beren İne Aydoğan2, Alptekin Güroğlu2, Mazhar Müezzinoğlu Tuna3, Mhetap Navidar Başaran3, Ayşen Akkurt4, Eda Ertürker5, Kadriye Aydın5, Sibel Gülüden6, Yasin Simsek7, Züleyha Karaca8, Merve Yılmaz9, Müjde Aktürk10, Inan Anaforoglu11, Nur Kebapçı12, Abdullah Taslınır13, Mustafa Kulaksızoglu14, Dilek Berker15, Tomris Erbas16 & Murat Faik Erdogan1

1Department of Endocrinology and Metabolism Diseases, Faculty of Medicine, Ankara University, Ankara, Turkey; 2Department of Endocrinology, Ankara Güven Hospital, Ankara, Turkey; 3Department of Endocrinology and Metabolism Diseases, Ankara Numum Education and Research Hospital, Ankara, Turkey; 4Department of Endocrinology and Metabolism Diseases, Faculty of Medicine, Uludag University, Bursa, Turkey; 5Department of Endocrinology and Metabolism Diseases, Faculty of Medicine, Adana Hospital, Basketen University, Adana, Turkey; 6Department of Endocrinology and Metabolism Diseases, Faculty of Medicine, Hacettepe University, Ankara, Turkey; 7Department of Endocrinology and Metabolism Diseases, Faculty of Medicine, Trakya University, Edirne, Turkey; 8Department of Endocrinology and Metabolism Diseases, Faculty of Medicine, Erciyes University, Kayseri, Turkey; 9Department of Endocrinology and Metabolism Diseases, Faculty of Medicine, Dokuz Eylül University, İzmir, Turkey; 10Department of Endocrinology and Metabolism Diseases, Faculty of Medicine, Gazi University, Ankara, Turkey; 11Trabzon Numum Education and Research Hospital, Trabzon, Turkey; 12Department of Endocrinology and Metabolism Diseases, Faculty of Medicine, Eskişehir Osmangazi University, Eskişehir, Turkey; 13Department of Endocrinology and Metabolism Diseases, Gülhane Military Medical Academy, Ankara, Turkey; 14Department of Endocrinology and Metabolism Diseases, Faculty of Medicine, Necmettin Erbakan University, Konya, Turkey.

Introduction
TURK-MEN study was carried out to evaluate the mutational analysis of so called sporadic and hereditary MTC patients in Turkey between 2008 and 2012.

Methods
Society of Endocrinology and Metabolism of Turkey (SEMT) sponsored ret genetic screening between July 2008 and January 2012 in 513 patients. We excluded family members of known patients who do not have ret mutation and patients with pheochromocytoma without mutation. We invited physicians of 319 eligible patients who had sporadic, familial MTC, MEN 2 or mutation carriers from known families and forms of 192 patients were attained. Analysis of exon 10, 11, 13, 14, 15 and 16 was performed.

Results
Between 2008 and 2012, among 513 patients whose blood samples were sent for ret genetic screening results, distribution of mutations among so called sporadic and hereditary MTC patients in Turkey between 2008 and 2012 was evaluated. The median duration of treatment was four circles (range 0.5–16). Discontinuation of treatment was noted in 14 out of 16 (87.5%) patients, who were unwilling to continue treatment due to side effects, and reported worsening of quality of life. Though most adverse events were grade 1 and 2, two patients experienced grade 4 serious adverse events. Life threatening were: stage 4 heart failure in one patient, reversible with treatment withdrawal, and stage 4 nose bleeding noted in another. More than 50% of patients reported fatigue, diarrhea, stomatitis and dermatologic disorders. Main laboratory abnormalities were anemia, neutropenia and hypertriglyceridemia. Dose reduction was required in five out of 16 patients. Concerning overall response, two patients showed partial response, nine stable and five progressive disease. Metastatic sites favouring response were lungs and liver.

Conclusions
Treatment with tyrosine kinase inhibitors should clearly balance benefits and risks of worsening patients good quality of life.

DOI: 10.1530/endoabs.32.P1090

P1091

Treating refractory thyroid cancer in the era of multitarget tyrosine kinase inhibitors

Lemniona Mathiopoulou, Maria Boudina, Alexandra Chrioulioud, Stylianos Mandanas, Elterpi Margaritiou, Konstantinos Georgopoulos & Kalliopi Pazaitou-Panayiotou

Theagenio Cancer Hospital, Thessaloniki, Greece.

Introduction
Tyrosine kinase inhibitors (sorafenib and sunitinib) have been used in treating refractory cases of thyroid cancer. The aim of our present study was to assess the efficacy of these agents in patients with refractory and progressive thyroid cancer, regarding patients’ quality of life, adverse events and response rates.

Patients and methods
We retrospectively analyzed data of adult patients with differentiated and medullary thyroid cancer (DTC and MTC) treated with either Sorafenib or Sunitinib. Disease progression was assessed according to RECIST criteria. Adverse events were documented and graded with the use of the NCI Common Terminology Criteria for Adverse Events. Patients received treatment until disease progression, serious-grade 4 adverse events or until unwilling to continue treatment due to adverse events.

Results
From April 2009 to October 2011 a total of 16 patients (nine males and seven females) were included. Six patients with MTC and ten patients with DTC were placed on tyrosine kinase inhibitors. The median duration of treatment was four circles (range 0.5–16). Discontinuation of treatment was noted in 14 out of 16 (87.5%) patients, who were unwilling to continue treatment due to side effects, and reported worsening of quality of life. Though most adverse events were grade 1 and 2, two patients experienced grade 4 serious adverse events. Life threatening were: stage 4 heart failure in one patient, reversible with treatment withdrawal, and stage 4 nose bleeding noted in another. More than 50% of patients reported fatigue, diarrhea, stomatitis and dermatologic disorders. Main laboratory abnormalities were anemia, neutropenia and hypertriglyceridemia. Dose reduction was required in five out of 16 patients. Concerning overall response, two patients showed partial response, nine stable and five progressive disease. Metastatic sites favouring response were lungs and liver.

Conclusions
Treatment with tyrosine kinase inhibitors should clearly balance benefits and risks of worsening patients good quality of life.

DOI: 10.1530/endoabs.32.P1091

P1092

Mutations and somatic changes in the genotype of rs2910164 in pre-miR146a are frequent in follicular thyroid carcinoma

Eleonora Vighi1, Elisa Piagnati2, Luca Roncati2, Vincenzo Rochira1,2, Elida Kara3, Bruno Marano4,5, Elisa Pignati2, Antonino Maorana4, Cesare Carani1,2 & Manuela Simonetti1,2

1Chair and Unit of Endocrinology & Metabolism, Department of Biomedical, Metabolic and Neural Sciences, University of Modena & Reggio Emilia, Modena, Italy; 2Integrated Department of Medicine, Endocrinology and Metabolism, Geriatrics, Azienda USL of Modena, NOCSAE of Baggiovara, Modena, Italy; 3Department of Diagnostic Medicine, Clinical and Public Health, University of Modena & Reggio Emilia, Modena, Italy.

Introduction
The mechanism underlying the development of follicular thyroid carcinoma (FTC), the second commonest thyroid tumor, is still unknown. An interesting hypothesis is that changes in the expression of multiple regulatory RNA (miR) genes may be a major mechanism in thyroid carcinogenesis. For example, several studies suggested that SNP rs2910164 in the pre-miR146a, a precursor of miR146a, might be correlated to papillary carcinoma. The aim of this study was the evaluation of the role of SNP rs2910164 in FTC tumorigenesis. Here for the first time we analysed the genotype frequencies of rs2910164 in both genomic and somatic DNA of patients affected by FTC.

Materials and methods
The region of pre-miR146a containing SNP rs2910164 was sequenced in both genomic and somatic DNA of patients affected by FTC. Somatic DNA was extracted from formalin-fixed-paraffin-embedded tissue, while genomic DNA was from peripheral blood. We compared the SNP distribution between patients’ genomic and somatic DNA (both unaffected and tumor tissue). In addition, patients’ genomic DNA was compared to 208 controls with negative thyroid sonography. SNP distribution was correlated to the clinical data.

Results
SNP rs2910164 undergoes mutations in the transition from genomic to somatic DNA in 37% of cases and from unaffected to tumor tissue in 31% of cases resulting in an increase of allele G frequency in tumor tissue ($P<0.05$, $\chi^2$ test), in which CC genotype was completely absent. The SNP distribution in the patients genomic DNA was the same as in negative controls ($P=0.9106$, $\chi^2$ test). No correlation between this SNP and clinical features was found.

Conclusion
Our data suggest that somatic GG and GC genotypes are associated with FTC, while CC homozygous state might have a protective role. This could result in modifications of target genes, the expression of which is affected by the SNP status.

DOI: 10.1530/endoabs.32.P1092

Endocrine Abstracts (2013) Vol 32
Interobserver agreement of thyroid imaging reporting and data system and realtime elastography for the assessment of thyroid nodules

Mireen Friedrich-Rust, Gesine Meyer, Nina Daub, Christian Berner, Eva Herrmann, Horst Anton Schroeter, Katharina Holzer, Lisa Voelkl, Stefan Zeuzem & Joerg Bojunga

1Department of Internal Medicine 1, J.W. Goethe-University Hospital, Frankfurt, Germany; 2Institute of Biostatistics and Mathematical Modelling, Faculty of Medicine, J.W. Goethe-University, Frankfurt, Germany; 3Praxis-Klinik für Diagnostik (PKD) am Staedel, Frankfurt; 4Department of General and Visceral Surgery, J.W. Goethe-University Hospital, Frankfurt, Germany; 5Institute of Pathology, J.W. Goethe-University Hospital, Frankfurt, Germany.

We studied 35 patients (11 men, 24 women) aged 50.9 and treatment outcome in patients with MTC. To define the relationship between biochemical parameters, disease progression, and 6.67% stage I – highlighting the aggressiveness. The onset of symptoms was 29.8 months before diagnosis, delayed in two cases by false negative FNAB. Most patients underwent total thyroidectomy with (60%) or without neck dissection (11.4%), in 22.9% partial thyroidectomy was performed and in two patients (5.7%) oncologic evaluation without surgery was recommended because of wide metastatic spread; 39.4% required multiple surgeries. Calcitonin decreased to 764 ± 2103 pg/ml at 3–6 months postop while the carcinoembryonic antigen decreased from 147.3 ± 283.9 to 5.35 ± 7.04 ng/ml. Only eight patients showed biochemical remission at 3–6 months postop: two patients were TMZ stage I at diagnosis, six were stage III. In patients with persistent disease, adjuvant therapies were tried: chemotherapy, external radiotherapy, internal radiotherapy, somatostatin analogues, radioiodine and IFN.

Conclusion Despite the potential for cure of MTC with timely intervention, optimal results are still achieved in a minority of cases, mostly due to the delayed diagnosis. After the ‘surgical’ window has passed, even a sustained multidisciplinary effort leads to poor results.

DOI: 10.1530/endoabs.32.P1094

Interobserver agreement of thyroid imaging reporting and data system (TIRADS) has been developed to improve patient management and cost-effectiveness by avoiding unnecessary fine needle aspiration biopsy (FNAB) in patients with thyroid nodules. However, since its publication in JCEM (2009) its clinical use is still very limited and its practicability in clinical practice is questioned. Realtime-elastography (RTE) 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 interobserver agreement of TIRADS and RTE. Three blinded observers independently scored stored images of TIRADS and RTE in 114 nodules of 114 patients. In addition, the diagnostic performance of TIRADS and RTE for the diagnosis of malignant thyroid nodules was calculated. Cytology and/or histology was available for all benign (n = 99) and histology for all malignant nodules (n = 15).

Results

The interobserver agreement between the three physicians was only weak for TIRADS categories 2–5 (Cohen’s k = 0.27, P = 0.000001) and TIRADS categories 2/3 vs 4/5 (Ck = 0.25, P = 0.0020). The interobserver agreement was substantial for RTE scores 1–4 (ck = 0.66, P < 0.000001) and very good for RTE scores 1/2 vs 3/4 (ck = 0.81, P < 0.000001). 92–100% of patients with TIRADS 2 had benign lesions, while 28–42% with TIRADS 5 had malignant cytology/histology.

The negative predictive value (NPV) was 92–100% for TIRADS using TIRADS categories 4 and 5 and 96–98% for RTE using score 3 and 4 for the diagnosis of malignancy, respectively. However, only 11–42% of nodules were in TIRADS-categories 2 and 3, as compared to 58–60% with RTE-score 1 and 2.

Conclusions

Interobserver agreement of TIRADS is only fair. TIRADS and RTE have high NPV for excluding malignancy in the diagnostic work-up of thyroid nodules. However, only 1/3 of FNABs could be avoided using TIRADS as compared to 60% using RTE. Prospective multicenter studies are needed to further evaluate the clinical utility of both methods.

DOI: 10.1530/endoabs.32.P1093

Medullary thyroid carcinoma – a narrow surgical window

Ruxandra Dobrescu, Diana Iacob, Bogdan Stanescu & Corin Badiu

1C.I. Pachon Institute of Endocrinology, Bucharest, Romania; 2"C. Davila" University of Medicine and Pharmacy, Bucharest, Romania.

Introduction

Occurring sporadically or as part of a familial syndrome, medullary thyroid carcinoma (MTC) is insidious in onset, aggressive in behavior and invariably a challenge to the clinician and surgeon.

Objective

To define the relationship between biochemical parameters, disease progression, and treatment outcome in patients with MTC.

Patient and methods

We studied 35 patients (11 men, 24 women) aged 50.9 ± 14.8 years, admitted to the National Institute of Endocrinology between 2004 and 2012 and diagnosed with MTC: six with MEN2A syndrome, three with familial MTC with documented RET mutation and 26 patients with sporadic MTC. Most patients presented with a thyroid lump or for screening if from a MEN2A kindred, seven with chronic diarrhea and 2-paraneplastic Cushing syndrome.

Results

Calcitonin at diagnosis was 1586 ± 1924 pg/ml (25 of 35 patients with available data); 36% were > 2000 pg/ml, the upper limit of the assay. TNM classification at diagnosis shows 56.67% of patients in stage IV, 33.33% stage III, 3.33% stage II, and 6.67% stage I – highlighting the aggressiveness. The onset of symptoms was 22.5 ± 29.8 months before diagnosis, delayed in two cases by false negative

DOI: 10.1530/endoabs.32.P1095

Radioactive iodine therapy in papillary thyroid carcinomas staged as T1

Pedro Marques, Daniel Macedo, Joana Pereira, Margarida Vieira, Valeriano Leite & Maria Bugalho

Portuguese Institute of Oncology, Lisboa, Portugal.

Introduction

131I therapy in patients with papillary thyroid carcinomas (PTC) ≤ 2 cm and without extrathyroidal extension (T1) depends on multifactorial analysis: age, multifocality, histological criteria, lymph node or systemic metastasis. The study purposes were analyze PTC-T1 and compare the groups treated only with surgery vs combined therapy (surgery and 131I).

Methods

Retrospective analysis of clinical files of PTC-T1 patients diagnosed between 2002 and 2006, and followed in Endocrinology Department of Portuguese Institute of Oncology, Lisbon. Patients were identified through South Regional Cancer Registry.

Results

A total of 453 patients (125 male and 328 female, mean age 47.4 ± 15.9 years) with papillary thyroid carcinoma were recruited. Those with stage I, II, III, IV was 57.6, 6.4, 14.8, 21.2%, respectively. The mean postoperative thyroglobulin level was 51.7 ± 251.8 ng/ml. The thyroglobulin level was stratified to I (1 < 2), II (between 2 and 10), III (between 10 and 30), IV (between 30 and 100), V (more than 100). The association between stage and thyroglobulin level was not significant (χ2, P = 0.0621). Postoperative thyroglobulin level was not significantly associated with the results of RAI ablation scan. During the follow-up period (mean 3.4 ± 2.6 years), 102 patients (22.5%) received repeated operation or RAI treatment for recurrent tumor or lymphnode metastasis. The recurrence rate in thyroglobulin level I, II, III, IV, V was 12.7, 20, 18, 27.5, 41.7%, respectively. The predictive effect of postoperative thyroglobulin levels for tumor recurrence was not statistically significant (logistic regression, P = 0.5985).

Conclusions

For patients with papillary thyroid carcinoma, post-operative thyroglobulin level was not associated with recurrence rate. Careful long-term follow-up was necessary even for patients with low thyroglobulin level.

DOI: 10.1530/endoabs.32.P1096
P1097
The role of radioiodine SPECT/CT in differentiated thyroid cancer

Emese Mezosi1, Laszlo Bajnok1, Karoly Rucz2, Csaba Weninger2, Erzsebet Horvath1, Janos Horaanyi2, Eszter Sekely3, Balazs Jaray3 & Karoly Zembo3

11st Department of Internal Medicine, University of Pecs, Pecs, Hungary; 2Department of Radiology, University of Pecs, Pecs, Hungary; 3Department of Nuclear Medicine, University of Pecs, Pecs, Hungary.

Introduction
Beside remnant ablation and treatment of known metastases, radioiodine treatment of differentiated thyroid cancer is suitable for the discovery of unknown or suspected metastatic disease. In this study, the clinical utility of SPECT/CT, a hybrid imaging method was evaluated after radioiodine therapy.

Patients and methods
Between July 2007 and March 2012, 260 investigations were performed at 188 patients. Male:female ratio was 47:141. Every patient was evaluated by whole body scanning (5 cm/min), planar (100K) and SPECT/CT imaging (SPECT: two detectors, 50 s/frame, 64 frame; CT: low dose, 16-slice helical CT, 120 kV, 50 mAs) 6 days after 1100-3700 MBq radioiodine treatment.

Results
Only remnant thyroid tissue was detected in 122 patients (47%). Absence of any radioiodine uptake plus a negative CT was found during 16 investigations (all were after repeated treatment). Pathological isotope accumulation was diagnosed with positive CT result in 96 cases (37%). Radioiodine uptake with suspected clinical significance without CT abnormality was found in 22 cases (8%). Radioiodine negative metastases were discovered during 21 investigations (8%). Lymph node, lung, bone and other metastases were diagnosed in 79, 41, 12 and 19 cases, respectively. Nonspecific radioiodine uptake was found during 23 investigations (8%). Radioiodine uptake plus a negative CT was found during 16 investigations (all were between 50 and 155 mCi).

From the 69 cases treated only with surgery, none presented risk histological criteria, namely aggressive histological variant, anaplasia, nodal or systemic metastasis. All are considered in complete remission.

Conclusion
Generally, PTC-T1 are associated with good prognosis. In the absence of metastasis and/or aggressive histological criteria, the benefit of 131I therapy is doubtful. A trend to reduce 131I therapies was noticed in this study.

DOI: 10.1530/endoabs.32.P1097

P1099
The prevalence, the tumorigenic role and the functional implications of rare BRAF alterations in a cohort of Italian patients with thyroid carcinomas

Raffaele Pezzani1, Susi Barollo2, Andrea Cristiani1, Marco Redaelli4, Laura Zambonin1, Beatrice Ruscillo5, Loris Bertazzia1, Mariangela Zane3, Carla Mucignat-Caretta4, Alessandro Bulfone3, Gianna Maria Pennelli2, Maria Rosa Pelizzo2, Franco Mantiero2, Stefano Moro2 & Caterina Mani1

1Endocrinology Unit, Department of Medicine, University of Padua, Padua, Italy; 2Biomedicine Sector, Center for Advanced Studies, Research and Development, Sardinia Technology Park Polaris, Pula (CA), Italy; 3Department of Molecular Sciences, University of Padua, Padua, Italy; 4Biomedicine Sector, Center for Advanced Studies, Research and Development, Sardinia Technology Park Polaris, Pula (CA), Italy; 5Endocrinology Unit, Department of Medicine, University of Padua, Padua, Italy.

Background
Papillary thyroid carcinoma (PTC) is the most common malignant tumor of the thyroid gland, accounting for 74-80% of all thyroid cancers. The T1799G>A transversion is an activating mutation of the BRAF oncogene that is common in conventional PTC and specific to it.

Aims
To study the prevalence, tumorigenic role and biomolecular implications of rare BRAF variants in a large cohort of patients.

Study design
A 1641 fine-needle aspiration biopsy samples were collected and subjected to BRAF mutation analysis: 494 were PTC. The rare genetic variants found were also analyzed by western blot to investigate their susceptibility in modulating fundamental signaling pathways, by immunofluorescence and by means of in silico analysis to evaluate their molecular role in large-scale exploration of conformational spaces.

Results
BRAF mutations were found in 271/494 (54.9%) of PTC. They were classic BRAF mutations: 494 were PTC. The rare genetic variants found were also analyzed by western blot to investigate their susceptibility in modulating fundamental signaling pathways, by immunofluorescence and by means of in silico analysis to evaluate their molecular role in large-scale exploration of conformational spaces. No significant alteration was seen in non-carriers. In group 1, we showed increased CYP24A1 expression ratio in conventional PTC and specific to it.

Conclusions
Our results suggest that ‘three-genes’ model completed with CYP24A1 might increase the efficiency of molecular diagnosis of papillary thyroid cancer. Also, we have demonstrated that certain pathological states within PTC are associated with altered gene expression.

DOI: 10.1530/endoabs.32.P1099
hobnail, one with tall cell variant and the last not yet operated); and c.1799_1814>A (p.V600_S605>D) in one patient (classic PTC variant).

Conclusions
This study delineated the prevalence, tumorigenic role and functional implications of rare BRAF alterations of thyroid carcinoma.

DOI: 10.1530/endoabs.32.P1099

P1100
Thyroglobulin in fine-needle aspiration wash-out diagnostic performance: a meta-analysis
Giorgio Grani & Angela Fumarola
Sapienza University of Rome, Rome, Italy.

Introduction
Differentiated thyroid cancer (DTC) has an excellent prognosis. However, DTC frequency metastasizes to cervical lymph nodes (CLN). In case of suspicious ultrasonography findings, the fine-needle aspiration (FNA) is usually required to confirm or exclude metastasis. The combination of FNA-cytology and thyroglobulin (Tg) measurements in the needle washout has been reported to increase the sensitivity of FNA in identifying lymph node metastases from DTC, particularly in the case of very small CLN. This assay is recommended by the revised American Thyroid Association guidelines for the follow-up of patients with DTC.

Methods
We have selected, through electronic databases, 28 original studies, published from 1992 through 2012. Each study deals with a small number of patients and is likely affected by selection bias. Pooled sensitivity, specificity, likelihood ratios (LR) and diagnostic odds ratio (dOR) were calculated.

Results
Including in the analysis all the studies with complete data (17 studies), the pooled sensitivity is 95.8% (95% CI 94.3–97%), specificity 91.5% (95% CI 89.1–93.5%), positive LR 15.33 (95% CI 6.97–33.70), and negative LR 0.06 (95% CI 0.04–0.11). However, there is a significant heterogeneity between studies, not due to threshold effect (Spearman correlation coefficient r = 0.146; P = 0.52). A meta-regression analysis demonstrated that the presence or absence of thyroid gland (evaluation before thyroidectomy or during after-surgery follow-up) is an important heterogeneity factor (rdOR 4.57; 95% CI 1.34–15.61; P = 0.02).

Conclusion
FNA-Tg measurement is a very accurate tool to detect CLN metastases from DTC. However, a better standardization of criteria for patient selection, analytical methods and threshold levels is required to provide useful data and to improve management of DTC patients.

DOI: 10.1530/endoabs.32.P1100

P1101
Thyroglobulin levels in the washout of lymph node fine-needle aspirate on patients with previous history of differentiated thyroid cancer
Sofia Gouveia¹, Cristina Ribeiro¹, Sandra Paiva¹, Márcia Alves¹, Joana Saraiva¹, Carolina Moreno¹, Daniela Guelho¹, Fátima Leitão² & Francisco Carrilho²
¹Endocrinology, Diabetes and Metabolism Department, Coimbra’s University Hospital, Coimbra, Portugal; ²Clinical Pathology Department, Coimbra’s University Hospital, Coimbra, Portugal.

Introduction
Our aim was to determine the comparable value of thyroglobulin in the washout of lymph node fine-needle aspirate (FNATg) and fine-needle aspiration biopsy (FNAB).

Materials and methods
We included 29 patients (37 FNAB) with history of differentiated thyroid cancer who underwent total thyroidectomy and were found to have suspicious cervical lymph nodes during follow-up. The referred population was evaluated on what concerns to gender, age, serum thyroglobulin, thyroglobulin antibodies, FNATg, FNAB and lymph node echographic features.
P1103
Evaluation of whole-body scan, stimulated thyroglobulin after thyroxine withdrawal vs recombinant TSH administration according to the risk groups of tumor recurrence
Mustafa Sahin, Berna Inge Aydogan, Bagdagül Yüksek, Murat Faik Erdogan, Sevim Gullü, Rifat Ensar, Demet Çorapçioğlu, Nilgün Baskal & Ali Riza Uysal
Department of Endocrinology and Metabolism Diseases, Ankara University Faculty of Medicine, Ankara, Turkey.

Background
Recombinant human thyroid-stimulating hormone (rhTSH)-stimulated serum thyroglobulin (Tg) (s-Tg) and (131)I whole-body scanning (WBS) are supposed to provide equal diagnostic information with thyroxine withdrawal (THW) at follow-up thyroid cancer patients without the symptoms of hypothyroidism. We aimed to compare the WBS and s-Tg levels after thyroxine injection and thyroid hormone withdrawal for tumor recurrence/persistence according to the risk groups.

Methods
The study included 150 patients (119 females, 31 males) prepared to diagnostic WBS with rhTSH or THW. Age, sex, WBS, sTg levels, recurrence and risk groups for tumor recurrence (ATA guidelines 2009) were assessed retrospectively.

Results
WBS was performed with THW in 86 patients and with rhTSH administration in 64 patients. Mean age and sex were not different between the groups. According to the risk groups for tumor recurrence, 71 patients were in low-risk group. In this group, 39 patients were prepared with THW and 32 patients were prepared with rhTSH for WBS. Mean diagnosis age and RAI doses were not different between the THW and rhTSH groups.

The peak TSH, s-Tg and Anti-Tg were significantly higher after THW compared with rhTSH administration. Both methods were equally effective for detecting metastatic or residual disease in low-risk group.

In moderate–high risk group (n: 79), 47 patients were prepared with THW and 32 patients were prepared with rhTSH for WBS. Mean diagnose age and RAI doses were not different between the groups. The peak TSH, s-Tg and Anti-Tg were also significantly higher after THW compared with rhTSH administration. Both methods were equally effective for detecting metastatic or residual disease in moderate–high risk group.

Conclusion
Both methods were equally effective for detecting metastatic or residual disease.

DOI: 10.1530/endoabs.32.P1103

P1104
Stimulated serum Tg ≥ 0.285 ng/ml in anti-Tg (−) cases had 3.087 times increased likelihood of recurrence of differentiated thyroid cancer: a single center experience
Ayşun Sentürk Yikılmaz1, Ümit Mousa2 & Aslı Nar2
1Ankara Egitim Arastirma Hastanesi, Ankara, Turkey; 2Baskent University Hospital, Ankara, Turkey.

Thyroid cancers constitute 2% of all cancer cases most of which are differentiated. Tumor size, lymph node metastases and thyroglobulin levels (Tg) in the follow-up period are among the major factors responsible for recurrence. In this study, we aimed to review our series of differentiated thyroid cancers and establish the risks of recurrence.

This study was carried out through a retrospective analysis of 393 differentiated thyroid cancer cases that were diagnosed in our department between January 2000 and December 2010. The demographic characteristics of the study group are seen in Table 1.

In the patients who had initial pathological lymphadenopathy, the recurrence risk was 2.76 times compared to the cases without pathological lymphadenopathy (P<0.001). The recurrence rate of male cases was 21 (30.4%). The cases with postoperative Tg (pre-radioactive iodine (RAI) ablation therapy) value ≥ 2 ng/ml increased the recurrence risk and mortality significantly (P=0.003, P=0.04 respectively). Stimulated Tg values ≥ 2 ng/ml 6–12 months following RAI treatment increased the risk of recurrence (P<0.001). Disease-free survival was also significantly shorter in this group (P<0.001).

Table 1 Demographic characteristics of the study group

<table>
<thead>
<tr>
<th>Number and percentage of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence group</td>
</tr>
<tr>
<td>Remission group</td>
</tr>
<tr>
<td>Histopathological analysis indicated papillary carcinoma</td>
</tr>
<tr>
<td>Follicular carcinoma</td>
</tr>
<tr>
<td>AJCC-2002 staging system</td>
</tr>
<tr>
<td>Stage I</td>
</tr>
<tr>
<td>328 (83.5%)</td>
</tr>
<tr>
<td>Stage II</td>
</tr>
<tr>
<td>32 (8.1%)</td>
</tr>
<tr>
<td>Stage III</td>
</tr>
<tr>
<td>27 (6.9%)</td>
</tr>
<tr>
<td>Stage IVA</td>
</tr>
<tr>
<td>6 (1.5%)</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>324 (82.4%)</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>69 (17.6%)</td>
</tr>
</tbody>
</table>

In our study, we established that tumor diameter, male sex, lymph node metastasis, stage III and higher stage, presence of capsule invasion, increase in the nodule size that was initially measured with ultrasonography, postoperative Tg values higher than ≥ 2 ng/ml, suppressed Tg higher than ≥ 0.3 ng/ml, stimulated Tg ≥ 2 ng/ml, stimulated serum Tg ≥ 0.285 ng/ml in anti-Tg (−) cases, serum Tg ≥ 5.6 ng/ml in the postoperative scan increased the recurrence risk. We recommend that these factors are kept under consideration in patient follow-up.

DOI: 10.1530/endoabs.32.P1104

P1105
Papillary thyroid carcinoma with focal hobnail features
Marija Igorëva Ryzhenkova, Elena Yurevna Furminskaja, Alexander Yurevich Abrosimov & Anna Petrovna Shinkarkina
Medical Radiological Research Center, Obninsk, Kaluga Region, Russia.

Background
Papillary thyroid carcinoma (PTC), the most common endocrine malignancy, is a tumor of indolent biological and clinical behaviour that usually has a good prognosis. Only a small percentage of patients are affected by aggressive variants of PTC: tall, columnar cell and diffuse sclerosing variants. These aggressive tumor subtypes are characterized by higher rate of local recurrence, regional and distant metastases than classic papillary PTC. Recently another clinically aggressive variant of PTC with hobnail features has been described. However prognostic significance of such focal hobnail component in classic papillary PTC has not been defined.

Cases report
In this study, we reviewed clinical, cytological, histological, immunohistochemical and molecular biological features of five classic papillary PTCs with focal ‘hobnail’ component. Tumors were diagnosed in two woman and three men from 14 to 49 years old (mean age was 31 years). Cytologically these cases were characterized by increased nuclear/cytoplasmic ratio of tumor cells, appearance of ‘a shoe nail’, separated arrangement of cells in smears, hyperchrome nucleus, cystic changes (dystrophy and cells degeneration, formation of ‘spherical’ complexes of tumor cells). Prevalence of focal ‘hobnail’ component in histological sections of PTCs was less than 20% of all tumor cells. Tumor size variation ranged from 0.2 to 1.5 cm (mean size was 0.85 cm). Regional metastases of PTC into the neck lymphatic nodes (LN) were diagnosed in all five patients. The BRAFV600E point mutation was detected in one of three cases analysed by direct sequencing of DNA extracted from frozen tumor tissue. The size of primary tumor with BRAFV600E was 1.5 cm. In four of five patients, the cytological material was obtained preoperatively by FNA from primary thyroid tumor, and metastatic tumors in LN.

Conclusion
PTC with focal hobnail component is characterized by the high frequency of regional metastases at the moment of primary tumor manifestation. Obviously that prevalence of BRAFV600E point mutation in PTC with focal hobnail features is similar as in classic papillary PTC without hobnail component.

DOI: 10.1530/endoabs.32.P1105

Endocrine Abstracts (2013) Vol 32
Pre-operative USG revealed nodules in 19 cases. Five of these patients had malignity. The malignity frequency was significantly higher in the nodule positive group than the no nodule group (26.3 vs 4.6% respectively, \(P<0.004\)). There was also no statistically significant TSH receptor antibody, Anti-TPO antibody titres and thyroid functioning difference between these groups (\(P>0.05\)).

Conclusions
We have determined the incidental thyroid cancer frequency in Graves’ disease patients population as 6.5%. Malignity rate grew higher when co-morbid nodules were also present (26.3%). We recommend that when total thyroidectomy patients are the case who is treated surgically for the Graves’ disease, especially if nodules are present, malignity risk must be taken into consideration.

DOI: 10.1530/endoabs.32.P1108

---

**P1107**

**Incidental thyroid cancer frequency in total thyroidectomy for the Graves disease patients and the effect of the presence of nodules on malignity rates**

Abbas Ali Tam\(^1\), Cafer Kaya\(^1\), Fevzi Balkan\(^1\), Pamir Eren Ersoy\(^2\), Samet Yalçın\(^2\), Gülen Kıyak\(^2\), Gülün Güler\(^2\), Rehyan Ersoy\(^2\) & Bekir Çakır\(^3\)

\(^1\)The Department of Endocrinology and Metabolism Disorders, Ataürek Training and Research Hospital, Ankara, Turkey; \(^2\)The Department of General Surgery, Ataürek Training and Research Hospital, Ankara, Turkey; \(^3\)The Department of General Surgery, Yıldırım Beyazıt University, The Center for Health Practice and Research, Ankara, Turkey.

Introduction
Our objective for the current review was to inquire the thyroid cancer frequency rate within the patients who have had total thyroidectomy procedure for definitive Graves’ disease treatment and to evaluate the contribution of the presence of nodules to malignity rates.

Materials and methods
The present study was conducted by scanning the data of 214 patients who were operated total thyroidectomy for permanent Graves disease treatment, retrospectively. The participants were assorted into sub groups as benign nodule group, malignant nodule group and no nodule group and afterwards evaluated. The groups were also compared in regards to demographic characteristics and laboratory data.

Findings
Fourteen of the 214 cases were diagnosed with cancer. The malignity prevalence was determined as 6.5%. The sex distributions were found to be statistically similar between the malignant and benign nodule groups (\(P=0.776\)). The malignity rate of the malignant nodule group was significantly higher than the benign nodule group (\(P=0.042\)). No significant difference seemed to be between the benign and the malignant nodule group in regards to median TSH receptor antibody levels (\(P=0.134\)). The cases were divided into two in regards to nodule presence.

DOI: 10.1530/endoabs.32.P1107

---

**P1108**

**Detecting somatic oncogene mutations in FNA samples of cold nodules in Hungary**

Bálint Tobíaš\(^1\), Bernadett Balla\(^1\), János P Kós\(^1\), János Horányi\(^2\), István Takács\(^1\), Zsolt Nagy\(^1\), Péter Horváth\(^1\), Balázs Járay\(^3\), Eszter Székely\(^3\), Roland Istók\(^1\), Tamás Székely\(^3\) & Péter Lakatos\(^1\)

\(^1\)1st Department of Internal Medicine, Semmelweis University, Budapest, Hungary; \(^2\)1st Department of Surgery, Semmelweis University, Budapest, Hungary; \(^3\)2nd Department of Pathology, Semmelweis University, 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/P-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 analyzed 250 consecutive FNA samples. In the examined samples, we found different genetic alterations (four BRAF, one NRAS, seven HRAS mutations and one RET/PTC3 rearrangement) in 13 of these cases. By cytology and histology, 19 cases were classified as malignant, from which we identified genetic alterations only in 5 (26.3%). In eight cases out of the 13 genetic alterations, no sign of cytological malignancy could be seen at the time of the study. In the 11 samples from 19 with papillary carcinoma, four BRAF (36.3%) and one RET/PTC3 (9.1%) mutations were detected. The rest of malignancies from 19 (follicular lesions and one medullary cancer) showed no genetic alterations. No PAX8/PPARgamma rearrangements were demonstrated in the 250 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.32.P1108

---

**P1109**

**Predictive value of preablation stimulated thyroglobulin in differentiated thyroid cancer**

Inmaculada Prior Sánchez\(^1\), Mª Ángeles Gálvez Moreno\(^2\), Carmen Tenorio Jiménez\(^2\), Mª Rosa Alhambra Expósito\(^2\), Raúl Ruiz Ortega\(^2\), Estefanía Moreno Ortega\(^2\), Juan Antonio Vallejo Casas\(^3\) & Pedro Benito López\(^3\)

Reina Sofia University Hospital, Córdoba, Spain.

Background
Previous studies have suggested that serum thyroglobulin (Tg) levels at the time of 131I remnant ablation just after thyroidectomy, could be a prognostic tumor marker in differentiated thyroid cancer (DTC).

Objective
The aim of this study was to evaluate if serum preablation Tg in the earliest postoperative period could be useful for predicting persistence or recurrence of disease.

Methods
This study was a retrospective analysis. We included 160 patients with DTC who underwent total thyroidectomy and received ablative therapy with I131 from January 2000 to December 2011. A stimulated Tg was measured just at the time of the first 131I therapy (preablation-Tg). We correlated this value with a stimulated Tg control (control-Tg) measured at the time of the diagnostic whole-body scan, performed approximately 6–12 months after preablation-Tg. Exclusion criteria were positive Tg antibody \( (n=9) \) and microcarcinoma \( (n=26) \). Follow-up was
performed according to the American Thyroid Association Guidelines published in 2009. The minimum follow-up period was 14 months.

Results
Sixty-three of 77 patients (82%) with preablation-Tg ≤ 3 ng/ml showed undetectable (≤ 1 ng/ml) control-Tg and 37 of 48 (77%) patients with preablation-Tg > 3 ng/ml showed detectable (> 1 ng/ml) control-Tg (P < 0.001). At follow-up, 72 of 91 (79%) with preablation-Tg ≤ 3 ng/ml showed remission and 20 of 28 patients (71%) who showed persistence/recurrence, had a preablation-Tg > 10 ng/ml (P < 0.001). The negative predictive value of recurrence in patients having preablation-Tg ≤ 3 ng/ml was found to be 98.4% (73 of 77 patients, P < 0.001).

Conclusion
Preablation-Tg levels correlated well with the control-Tg levels. A preablation-Tg ≤ 3 ng/ml is a favorable prognostic factor in DTC.

DOI: 10.1530/endoabs.32.P1109

P1110
Concurrent follicular and columnar cell variants of papillary thyroid carcinoma characterized by different BRAF status and metastatic properties: a case review
Alexander Abrosimov1,2 & Anna Shinkarkina1
1 Medical Radiological Research Centre, Obninsk, Kaluga Oblast, Russia; 2Endocrinological Research Centre, Moscow, Russia.

Papillary thyroid carcinoma (PTC) is a malignant tumour of follicular cell origin that is characterized by a broad diversity of histological variants. A genesis of multifocal PTC may be explained by both intrathyroid tumour dissemination and multiple focuses of tumour origination. A combination of two different focuses of PTC characterized by various molecular alterations of tumour cells in one thyroid could be rarely occurred. Follicular variant has similar clinical behaviour and prognosis as classic papillary PTC. Columnar cell variant was initially defined as an aggressive lesion by Evans in 1986. Here, we present a case review of concurrent follicular and columnar cell variants with molecular analysis of BRAF status in tumour cells of different PTC histotypes.

Female of 62 years old was admitted to the Medical Radiological Research Centre with complaints of pain in a right thigh. A tumour of right femoral bone was diagnosed by X-ray examination. A core tumour biopsy revealed metastasis of thyroid carcinoma that cells were immunopositive for thyroglobulin and TTF-1. Thyroid ultrasonography showed two nodular lesions in right lobe and isthmus. Histological study of the thyroid after thyroideectomy revealed follicular variant in isthmus and columnar cell variant of PTC in right lobe. Histological review of resected right femur with metastatic tumour showed columnar cell type of PTC. Molecular study of DNA extracted from two different tumours revealed wild type status of BRAF in follicular variant and BRAFV600E point mutation in columnar cell variant.

Columnar cell variant of PTC is more aggressive type of thyroid carcinoma in a patient with two concurrent PTC variants (follicular and columnar cell). In contrast with follicular variant columnar cell variant of PTC was characterized by distant bone metastases and BRAFV600E point mutation.

DOI: 10.1530/endoabs.32.P1110

P1111
Thyroglobulin as an early marker of persistent/recurrent disease in patients with differentiated thyroid carcinoma (DTC)
Anna Masó Aulinas1, Cristina Comi Colom2, Lilian Mathison Mendoza1, Valeria Aragón Alcantara1, Eugenia Matute Mato3, Rosa Pla Corcoy1,3, Ignasi Saladich Gich1, Jose Espinosa Rodriguez2 & Cintia Blanco Gonzalez1,2
1Endocrinology and Nutrition Department. Santa Creu & Sant Pau Hospital, Barcelona, Spain; 2Endocrinology Unit, Dus de Maig Hospital, Barcelona, Spain; 3Biomedical Research Networking Centre on Bioengineering, Biomaterials & Nanomedicine: CIBER-BBN-EDUAB-HSP group, Spain; 4Clinical Epidemiology Department. Santa Creu & Sant Pau Hospital, Barcelona, Spain.

Introduction
Several clinical and molecular markers can be used to establish risk at the time of diagnosis in DTC. Thyroglobulin (Tg), which is essential in follow up, could be an early marker to identify risk patients. Around 25% of patients require 18 months or longer to have undetectable Tg. The presence of Tg antibodies (TgAb) invalidate the follow up of DTC via Tg and this is usually associated with a poor prognosis.

Aim
To evaluate the role of Tg after surgery and before radiiodine treatment, and the presence of TgAb as markers of persistent/recurrent disease in DTC.

Patients and methods
Retrospective study of 165 patients with DTC (1997–2010): women 78.2%, age at diagnosis 47.9 +/- 16.26, medium follow up 4.8 +/- 3.74 years. We performed a multivariate (logistic regression) analysis including Tg after surgery and before radiiodine treatment and other known prognostic variables. We divided Tg into tertile (cut-off: 1.7 µg/l, 13.6 µg/l) excluding TgAb positive at first before adding it later. We performed a ROC curve to identify cut-off level of Tg. Statistical analysis was performed with SPSS 19.0.

Results
In the multivariate analysis excluding TgAb positive, Tg in higher tertile is the unique predictive variable of persistent/recurrent disease at 18–24 months (RR 21.67). Adding positive TgAb, the predictive variables are Tg (RR 23.04) and presence of TgAb (RR 112). The ROC curve shows a cut-off of Tg after surgery and before radiiodine treatment of 5.55 µg/l that identifies persistent/recurrent disease (S 81, E 57.5, NPV 92.5 and PPV 31.5% [AUC 0.809]).

Conclusions
In this serie, Tg value after surgery and before radiiodine treatment and the presence of TgAb are predictive variables of recurrent/persistent disease at 18–24 months. Tg has a predictive value and could be a useful marker to stratify risk at the time of diagnosis.

DOI: 10.1530/endoabs.32.P1111

P1112
Ultrasound guided enolization as a therapeutic alternative in local recurrences of papillary thyroid carcinoma
Tomás Martín Hernández1, José Pérez Rodríguez1, Natividad González Rivera1, Alberto Torres Cuadra1, Clara García García1 & Virginia Martín Manzano2
1Endocrinology and Nutrition Clinical Unit, Virgen Macarena University Hospital, Seville, Spain; 2Medicine School. Seville University, Seville, Spain.

Introduction and objectives
Multiple surgeries are associated with many complications in the local recurrence of papillary thyroid carcinoma. Our objective is to evaluate the efficiency of the enolization in the recurrent metastatic cervical lymph nodes in patients with limited nodal disease.

Material and methods
We studied 13 patients (six males and seven females) with a mean age of 43±1.4 years with papillary thyroid carcinoma intervened (total thyroideectomy) in our follow-up, they present nodal recurrence (23 lymph nodes). Seven had previous lymphadenectomy (1–3) and they had received a mean I-131 dose of 238.46±71.25 mCi. In four cases, the anti-Tg Ab were elevated where the PET was positive. All of them showed pathological levels of Tg-FNAB (1.7–15 342 ng/ml). Guided by ultrasound, we injected absolute ethanol (20-30% of total lymph node). Were required for 1–3 enolizations spaced in 3–4 months until the absence of vascular flow.

Results
The mean nodal volume was 0.155±0.071 cm³. The initial mean thyroglobulin ONX was 5.70±5.08 ng/ml. We observed a nodal volume reduction with no vascular flow in all cases with an average volume of 0.075±0.054 cm³ postenolization (~0.0080 cm³, P < 0.0001). We got a reduction > 30% in 18 lymph nodes, > 50% in 13, > 70% in nine and disappearance in six. We also observed a decrease in average thyroglobulin levels to 3.47±4.17 ng/ml (~2.23~1.90, P < 0.01). In six of nine patients, the reduction in the levels of thyroglobulin was > 50%. All without evaluate the cases with Tg Ab positive. No significant adverse reactions were observed.

Conclusions
The ultrasound-guided enolization is presented as an excellent alternative to surgery for local recurrence of thyroid papillary carcinoma in selected cases where surgery is not recommended.

DOI: 10.1530/endoabs.32.P1112
**P1113**

Liquid preparation cytology for evaluation of thyroid nodules

Elahi Keyhani1,2, Sassan A Sharghi3, Rana Amini4, Sina A Sharghi4 & Bagher Larjani5

1Genetics Research Center-University of Social Welfare & Rehabilitation Sciences, Tehran, Iran; 2Sepad Pathobiology Laboratory, Karaj, Iran; 3Research Institute of Endocrinology & Metabolism-Tehran University of Medical Sciences, Tehran, Iran; 4Tehran University of Medical Sciences, Tehran, Iran.

**Introduction**

FNA (fine needle aspiration) is a highly sensitive and specific procedure in evaluating of thyroid nodules. There are several options for processing the FNA specimen such as direct smears, cell block preparations (CBP) and liquid base preparations (LBP); the latter has become more popular due to its easy transport, fast protocol and also the possibility to study different parts of the specimen. In this study, we compare the results of cell block and liquid base preparation in the same samples.

**Design and methods**

FNA performed for 80 patients with minimally 1 cm diameter solitary nodule or a prominent nodule on a multinodular background (excluding hot nodules), the obtained samples used to prepare direct smears, cell blocks and liquid preparations. The microscopic results recorded considering the following: cellularity, blood, colloid and macrophages.

**Results**

Forty-five of the samples (56.25%) show the same results in both CBP & LBP which confirmed direct smear findings. In 11 samples (13.75%), the CBPs, and in 24 samples (30%) the LBPs were more informative and diagnostic.

**Conclusion**

Totally in about 70% of cases, LBC method had sufficient diagnostic microscopic data so the liquid base method should be trusted due to its easier procedure & cleaner slide background. It could be used instead of CBP and in association with direct smears for precise evaluation of thyroid nodules.

DOI: 10.1530/endoabs.32.P1113

---

**P1114**

Prevalence of hypovitaminosis D in patients with papillary thyroid carcinoma (PTC)

Aldona Kowalska1, Danuta Gasior-Perczak2, Iwona Palyga1, Monika Siolek2, Anna Sluszniak1, Ryszard Mezyk1 & Stanislaw Gozdz1

1Department of Endocrinology and Nuclear Medicine, Holycross Cancer Centre, Kielce, Poland; 2Genetic Clinic, Holycross Cancer Centre, Kielce, Poland.

**Introduction**

The correct 25-hydroxy vitamin D (25(OH)D) level plays a key role in the proper supply of vitamin D for the organism. Vitamin D deficiency may lead to an increased risk of development of various neoplasms, including papillary thyroid carcinoma (PTC).

**Aim**

Evaluation of the prevalence of vitamin D deficiency in patients with PTC and analysis of the relation between 25(OH)D levels and age, sex, place of living, severity of the disease, and presence of the CHEK2 mutation.

**Material**

The study consisted of 168 patients with PTC: F:149 (88.7%), M: 19 (11.3%), aged 19–78 years. Mean age 52.3 (SD 13.6) years.

**Methods**

Exams were conducted during autumn. Plasma levels of 25(OH)D were measured by the RIA method. Prevalence of vitamin D deficiency in the studied group and age, sex, place of living, severity of the disease, and presence of the CHEK2 mutation.

**Results**

25(OH)D < 30 ng/ml deficiency was present in 101 patients and extremely low vitamin D < 10 ng/ml in three patients. Vitamin D deficiency was present in 62.1% of inhabitants of cities and 65.1% of inhabitants of villages, 63.3% women and 63.2% men, 63.8% patients in I stadium of the disease, 58.8% – II, 57.7% – III, 85.7% – IV, and 56.2% patients with CHEK2 mutation and 69.5% without mutation.

No correlations were found between 25(OH)D levels, prevalence of 25(OH)D deficiency and age, sex, place of living, severity of the disease, and presence of the CHEK2 mutation.

**Conclusions**

More frequent 25(OH)D deficiency due to CHEK2 gene mutation or severity of the disease was not found. Results suggest the need for prophylaxis programme of the vitamin D deficiency in patients with PTC, but do not allow to point to vitamin D deficiency as the factor potentially influencing the onset and course of the disease.

DOI: 10.1530/endoabs.32.P1114

---

**P1115**

Primary thyroid lymphoma – report of four cases

Joana Couto, Raquel Martins, Ana Paula Santos, Luis Leite, Ângelo Martins, Luis Lencastre, Cristina Sanches, Manuel Jácome, Rui Henrique & Isabel Torres

Portuguese Institute of Oncology of Porto, Porto, Portugal.

**Introduction**

Primary thyroid lymphoma (PTL) is responsible for 0.6–5% of all cases of thyroid cancer and less than 2% of all extranodal lymphomas. PTL is more common in elderly women and are commonly of B-cell origin. Current treatment regimens for PLC consist of chemotheraphy and external beam radiation. Surgery plays an important role, including the control of symptoms in large obstructive lymphomas.

**Aims and methods**

Retrospective data review of pts with PTL diagnosis followed at our Institution’s Endocrinology Department.

**Case reports**

Four female patients (pts), with 53–78 years (median 65). Three pts presented with a multinodular goiter, one pt with a solitary thyroid nodule and all had compressive symptoms. Thyroid function tests were normal at presentation and lymphocytic thyroiditis (LT) had been previously diagnosed in one pt. Cytological exam was suspicious for lymphoma in one case. Two pts were submitted to total and two pts to subtotal thyroidectomy. Histopathology revealed diffuse large B-cell lymphoma in two pts, a marginal zone B cell lymphoma and a Burkitt’s lymphoma. LT was described in two patients’ report. Three patients received combination chemotherapy (CHOP regime in two pts and BFM protocol in one pt). One pt received local radiotherapy. Imaging modalities revealed other areas of involvement in two pts. Three patients showed complete response to treatment and in one pt chemotherapy had to be stopped because of its toxicity.

**Discussion**

Primary lymphoma is a rare type of thyroid cancer and its cytological diagnosis can be complex because of the discrimination from LT, which is associated with an increased risk of TPL. Thyroid lymphoma should be suspected in the presence of a rapidly enlarging neck mass causing compressive symptoms, mostly in elderly woman with a LT diagnosis. The disease can often be cured without the need for extensive surgery if recognized early.

DOI: 10.1530/endoabs.32.P1115

---

**P1116**

Treatment, follow up and prognostic factors of papillary microcarcinoma

Alper Celil Udangululli1, Eda Demir Oner1, Elif Ozyemir2, Rifki Ulcer1, Gulten Kiyak3, Pamir Ezen Esroy4, Sumeet Yalcin1, Gulten Guler4, Reyhan Esroy4 & Bekir Cakir4

1Yildirim Beyazit University Ankara Ataturk Education and Research Hospital Endocrinology and Metabolism Diseases Department, Ankara, Turkey; 2Yildirim Beyazit University Ankara Ataturk Education and Research Hospital Nuclear Medicine Department, Ankara, Turkey; 3Yildirim Beyazit University Ankara Ataturk Education and Research Hospital General Surgery Department, Ankara, Turkey; 4Yildirim Beyazit University Ankara Ataturk Education and Research Hospital Pathology Department, Ankara, Turkey.

**Introduction**

The incidence rate of papillary thyroid microcarcinoma (PTMC) has almost doubled during the recent years but treatment and follow up is still a matter of debate. In this study we aimed to analyze clinical and histopathological risk factors at the time of diagnosis and to observe their implications for treatment, follow up and prognosis.

**Patients and methods**

Two hundred forty-eight PTMC patients were included in this study. The age, sex, the method of diagnosis (incidental or with a clinical suspicion), cervical lymph node metastases and relapse and/or distant metastases during follow up were retrospectively recorded.

Endocrine Abstracts (2013) Vol 32
Macrofollicular variant of papillary thyroid carcinoma: an uncommon entity

Arzu Gedik1, Merve Yilmaz1, Tevfik Demir1, Meriş Guray Durak2, Ahmet Omer Ikiz2, Mehmet Ali Kocör2, Ozhan Ozdogan3, Fırat Bayaktar1 & Abdurrahman Comlekçı1
1Endocrinology Department, Dokuz Eylül University Medical Faculty, Izmir, Turkey; 2Pathology Department, Dokuz Eylül University Medical Faculty, Izmir, Turkey; 3Department of Ear Nose Throat and Head & Neck Surgery, Dokuz Eylül University Medical Faculty, Izmir, Turkey; 4General Surgery Department, Dokuz Eylül University Medical Faculty, Izmir, Turkey; 5Nuclear Medicine Department, Dokuz Eylül University Medical Faculty, Izmir, Turkey.

Background
Macrofollicular variant (MV) is a rarely seen variant of papillary thyroid carcinoma (PTC). We herein present clinical characteristics of four patients carrying this variant of PTC. Case 1: 62-year-old female patient underwent total thyroidectomy (TT) due to euthyroid multinodular goiter (MNG) with a cytology of ‘indeterminate nodule’. The pathology revealed ‘papillary thyroid microcarcinoma MV with a diameter of 9 x 9 mm, without capsule or LVI’.

Case 2: 61-year-old female patient underwent TT due to toxic MNG. Pathology revealed ‘thyroid papillary microcarcinoma MV with a diameter of 9 x 9 mm, without capsule or LVI’. Case 3: 60-year-old man underwent TT due to euthyroid MNG with pressure symptoms on his neck. Pathology revealed bilateral multiseptate PTC; a focus of MV with a diameter of 2 x 2 cm in the right lobe; two foci of classical variant with diameters of 3 x 2 and 2 x 2 mm in the left lobe. No local/distant metastasis were identified in cases 1, 2 and 3. Case 1 and 2 were started TSH suppression therapy and case 3 received radioactive iodine (RAI) and suppression therapy afterwards. Case 4: 50-year-old male patient with a previous diagnosis of metastatic PTC after left cervical lymph node (LN) excision, underwent TT, central and lateral neck dissection. Pathology revealed ‘PTC MV focus of 2.7 cm with capsule and LVI, and metastatic LN on left lateral neck (biggest in diameter 5 cm) and left paratracheal compartment (5.5 cm in diameter)’. No distant metastases were identified. He has been referred for RAI ablation therapy.

Conclusion
Macrofollicles in PTC-MV may cause diagnostic pitfalls during cytology which may be incorrectly defined as benign goiter. The presence of macrofollicles > 200 μm in > 50% of the cross-sectional area is pathognomonic for PTC-MV. Despite its rarity and benign course, these patients should be evaluated for local/distant metastases.

Angiosarcoma of the thyroid gland: a case report
Entella Pucà1, Kadır Barak Koço1, Ugur Gozalan1, Selim Erektol1, Ema Lumi2 & Edmond Pucà1
1American Hospital II, Tirana, Albania; 2Regional Hospital Korca, Korca, Albania; 3UHC Mother Teresa, Tirana, Albania.

Angiosarcoma of the thyroid is a rare and aggressive primary malignant tumor of the thyroid: it rarely occurs in that organ and most of these occur mainly in patients from the mountainous Alpine regions. We report a case of 68-year-old female who presented at our hospital with a rapidly enlarging neck mass associated with compressive symptoms. On clinical examination, the thyroid gland appeared firm during the acts of deglutition. The results of thyroid function tests were for subclinical hyperthyroidism. Ultrasound examination and CT scan showed multinodular goitre with a suspicious nodule from the right thyroid lobe. Fine needle aspiration cytology of the thyroid was suggestive of anaplastic thyroid carcinoma. A total thyroidectomy was performed. Grossly, the right lobe and left lobe measured 8 x 7 x 4 cm and 8 x 8 x 7 cm. Macroscopically, the cut surface showed a bulging solid hemorrhagic dark red mass, measuring 4.8 x 3.2 x 2.5 cm, at the lower pole of the right lobe. The immunohistochemistry showed CD31 and CD34 positivity and thyroglobulin, calcitonin, and TTF-1 negativity indicating an angiosarcoma. The patients died within 2 months following up from pulmonary hemorrhage.

In conclusion, this case illustrates that thyroid angiosarcoma is a distinct entity and should be considered and included as a differential diagnosis of poorly differentiated thyroid neoplasms also outside the mountainous Alpine regions.

Postoperative stimulated thyroglobulin levels in thyroidectomized patients with differentiated thyroid cancer
Ricardo Batanero, Estela Elias, Ana Rosa Molina, Sonia Gurtambide & Javier Santamaria
Hospital Universitario Cruces, Barakaldo, Vizcaya, Spain.

Introduction
The presence of undetectable serum levels of stimulated thyroglobulin (Tg) with negative imaging tests is the criterion used to define remission in low-risk differentiated thyroid cancer (DTC). Most guidelines recommend 131-I ablation after thyroidectomy to remove any possible residual thyroid tissue. Our aim was to know how often undetectable Tg levels are achieved before ablation to avoid unnecessary radiation treatments.

Patients and methods
One hundred and eighteen patients (106 women and twelve men, age 15–83 years) with low-risk DTC who underwent total thyroidectomy from 2005 to 2011 were included. Tg, anti-Tg antibodies (TgAb) and TSH were analysed before and the fifth day after a dose of recombinant human TSH administration. They were measured in an Immulite® 2000 (Tg functional sensitivity: 0.9 ng/ml) 6-18 weeks after the surgery. Subsequently, a dose of 100 mcg of 131-I was administered to all patients and other possible treatments were applied when necessary. A correlation between postoperative stimulated Tg concentration and clinical situation at the end of the follow-up (25.6 ± 15.6 months) was performed.

Results
Eleven patients with positive TgAb were excluded. Tg levels were undetectable in 50 patients (47%), 1–10 ng/ml in 42 (39%) and > 10 ng/ml in 15 (14%). At the end of the study, there was no evidence of recurrence in the 50 patients with undetectable postoperative Tg. Remission criteria were met in 39/42 and 9/15 patients with Tg between 1–10 and > 10 ng/ml, respectively.

Conclusions
In near half of the patients with low risk DTC 131-I therapy is not necessary to achieve undetectable Tg levels after total thyroidectomy. An undetectable postoperative stimulated Tg predicts the absence of recurrence during the long term follow-up. 131-I ablation should not be necessarily performed in all the patients with low-risk DTC.

MIBI – spect scintigraphy in the presurgical assessment of thyroid lesions with indeterminate cytology
Elena Goldin1, Pinchas Klein1, Vladimir Sopov2, Sergey Mekhmandarov2, Galiy Avize3, Alona Meir3, Pier Chouraqui4 & Anat Jaffe4
1Endocrinology Unit, Hillel Yaffe Medical Center, Hadera, Israel; 2Radiology Department, Hillel Yaffe Medical Center, Hadera, Israel; 3ENT Department, Hillel Yaffe Medical Center, Hadera, Israel; 4Pathology Department, Hillel Yaffe Medical Center, Hadera, Israel.
P1121 Clinical and biochemical criteria for the prognosis of small medullary thyroid carcinomas
Katerina Saltiki, Gianna Rentziou, Vasiliki Vasileiou, Anastasia Athanasiadou, Eleni Anastasiou & Maria Alevizaki
Athens University School of Medicine, Athens, Greece.

Introduction
Small medullary thyroid carcinomas (sMTCs) ≤ 1.5 cm are frequently diagnosed, occasionally as incidental findings in surgical and autopsy specimens. Their clinical course varies. We examined whether tumor size is a predictor of clinical behavior.

Methods
One hundred and one sMTC patients (36.6% males, 47.1% familial) followed-up for 0.9–15 years. Patients were classified according to tumor size (cm) in groups: 0.1–0.5 (n = 25), 0.6–0.8 (n = 22), group 3: 0.8–1.0 (n = 23), group 4: 1.1–1.5 (n = 31).

Results
Familial cases did not differ from sporadic ones concerning stage at diagnosis or outcome. Preoperative and postoperative calcitonin levels were positively associated with tumor size (P < 0.001). At diagnosis, capsular and lymph node invasion were more frequent in groups 3 and 4 (P < 0.002, P < 0.001 respectively).

P1122 Histopathologic characterization of differentiated thyroid carcinoma in an area of Basque country
Mº Angeles Vicente Vicente, Pilar Sierra Polo, Carmen Cabrejas Gómez, IrisKun Olaziala Iregi, Natalia Gonzalez Cabrera, Clara Rosario Fuentes Gómez & Mº Angeles Antón Miguel
Hospital Universitario Araba, Vitoria-Gasteiz, Spain.

Background
The most common type of thyroid cancer is the well-differentiated thyroid carcinoma (DTC) and that includes papillary (PTC) and follicular carcinoma (FTC). The PTC would represent 50–90% and the FTC over 15–30%. Within the PTC, the most frequent is the classical variant (over 80%), followed by follicular variant (10%) and the rest of variants (<10%). Furthermore, there are differences between PTC and FTC in age at diagnosis, local extension, multicentricity and the presence or absence of lymphadenopathy. Our aim was to analyze the prevalence of the different variants of CDT in an area of the Basque Country and the histopathologic characteristics of the sample.

Methodology
We studied the medical records of 110 patients diagnosed with differentiated thyroid cancer, obtained from hospital tumor registry between the years 2005–2012. Using SPSS we performed a descriptive analysis of the sample and compared means.

Results

<table>
<thead>
<tr>
<th>N=110</th>
<th>PTC = 89 (81%)</th>
<th>FTC = 21 (19%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>54 ± 17</td>
<td>51 ± 19</td>
<td>n.s.</td>
</tr>
<tr>
<td>Average size</td>
<td>15.7 ± 13</td>
<td>33.8 ± 16</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Multicentricity</td>
<td>31%</td>
<td>15%</td>
<td>n.s.</td>
</tr>
<tr>
<td>Dedifferentiation</td>
<td>2%</td>
<td>10%</td>
<td>n.s.</td>
</tr>
<tr>
<td>Local extension</td>
<td>18%</td>
<td>10%</td>
<td>n.s.</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>20%</td>
<td>0%</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Histotypes</td>
<td>Class I: 38%</td>
<td>Minimal invasive 67%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Class II: 38%</td>
<td>Widely invasive 14%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Class III: 24%</td>
<td>Diffuse sclerosing 5%</td>
<td>Oncocytic 14%</td>
</tr>
<tr>
<td></td>
<td>Columnar 1%</td>
<td>High cell 1%</td>
<td>Trabecular 5%</td>
</tr>
<tr>
<td></td>
<td>Clear cell 0%</td>
<td>Mixed 17%</td>
<td></td>
</tr>
</tbody>
</table>

No significant differences among the different histotypes of each group in terms of age at diagnosis and tumor size were found. There was also no correlation between size and age at diagnosis.
P1124

A rare case of nonesecretory medullary thyroid carcinoma
Florbela Ferreira1, Mafalda Marcellino2, Ana Wessling1, Ema Nobre1, Valeriano Leite2, Isabel Carmo3
1Santa Maria Hospital, Lisbon, Portugal; 2Predicato Hospital, Lisbon, Portugal.

Introduction
Medullary thyroid carcinoma (MTC) is a rare form of thyroid cancer, making up about 5-6% of all cases. It is characterized by the synthesis and secretion of calcitonin (CT). Measurement of CT has low specificity but is a highly sensitive method for the detection of MTC. MTC with normal or only slightly elevated CT is a rare occurrence and there are few such reports in the literature.

Case report
A 63-year-old male patient was referred to the Endocrine consultation for evaluation of a solid, solitary, right lobe thyroid nodule, 38×30 mm in diameter. There were no suspiciously enlarged nodules on the neck sonogram. The nodule had first been detected 2 years before and grew slowly since then. Fine needle aspiration (FNA) revealed a benign cytology. Serum TSH and FT4 were normal, with increased anti-peroxidase antibodies (826 IU/mL). Serum calcitonin was 15.4 ng/L and CEA was 2.4 µg/L. The patient underwent right lobectomy.

Pathology analysis revealed MTC. There was no vascular nor capsular invasion. The frozen section specimens were sent to another Pathology Department of a public Oncology Hospital, which confirmed the diagnosis of MTC. Postoperative CEA level was <0.2 ng/mL. Habitus marfanoid and mucosal neuromas were not apparent. Urinary catecholamines and metanephrines were normal, as were serum calcium and PTH. There was no family history of endocrine disease. The results of the genetic testing of the RET gene are still pending.

Conclusions
The features of the sonogram and FNA test and the minimally increased level of CEA in the context of goiter and auto-immune thyroiditis did not raise suspicion of thyroid cancer. This is one of the rare cases described in the literature of MTC with almost normal CEA.

P1125

Coexistent medullary thyroid carcinoma and multifocal papillary thyroid microcarcinoma in a patient with chronic autoimmune thyroiditis
Ionela Pascanu1, Radu Neagoe2, Oana Capraru1 & Angela Borda1,2
1University of Medicine and Pharmacy, Targu Mures, Romania; 2Mures County Emergency Clinical Hospital, Targu Mures, Romania.

Introduction
The association between medullary (MTC) and differentiated thyroid cancer (DTC, with the most frequent form of papillary thyroid carcinoma, PTC) is rare and can be observed in two main settings: a collision tumor (that is, a tumor with two separate and different components) or a mixed tumor showing dual differentiation.

Case report
A 58-year-old woman, affected by euthyroid multinodular goiter came to our observation for a second opinion regarding the surgical indications for their goiter. The thyroid antiperoxidase antibodies titer was elevated, ATPO: 5.61. An ultrasound scan revealed diffuse thyroid enlargement with a suspicious nodule (hypoechoic, with irregular margins, calcifications and intranodular hypervascularization) of 9.8/11.7 mm, recently described in the upper third of the left thyroid lobe. In both lobes, other micronodules hypo- to isoechoic were also described. The serum calcitonine (CT) was 78, repeated 82 pg/ml (normal values ≤ 2 pg/ml) and calcinoectin antigen (CEA) was also elevated. The fine-needle aspiration cytology was non-diagnostic and patient was referred for surgery for total thyroidectomy with central compartment neck dissection. The histological examination confirmed the diagnosis of medullary thyroid cancer, showing a lymphocytic intrafollicular infiltration and multiple occult follicular variant of papillary microcarcinoma in both lobes. One of this microcarcinoma was adjacent to the medullary carcinoma. No lymph node metastases were found. The serum levels of CT and CEA decreased to normal after the operation. Molecular analysis of the RET proto-oncogene was performed.

Conclusions
In our case, the simultaneous occurrence of MTC and multifocal PTC has the features of a collision tumor, although the close relationship of one of the foci of PTC with MTC has rise the hypothesis of a mixed tumor.

P1126

BRAF V600E mutation in papillary thyroid cancer: clinical and pathological features. Is there any role in tailoring initial treatment?
Amelia Oleaga, Fernando Gohi, Miguel Paja, Natalia Iglesias, Elena Fuertes, Aitzol Lizarraga, Angel Gomez Palacios & Ramon Elorza Basurto Hospital, Bilbao, Vizcaya, Spain.

Introduction
BRAF V600E mutation is the most frequent detected genetic change in papillary thyroid cancer (PTC) and its presence has been related to aggressive clinical and pathological features. Lymph node metastases (LNMs) are common in PTC and are associated with an increase in loco-regional recurrence. However, prophylactic lymph node dissection is not routinely performed because of high rate of surgery complications. Therefore, there is a need to find a good marker to decide the extent of initial surgery.

Methods
We evaluated 31 patients (77.5% females) with pathological diagnosis of PTC. All of them underwent total thyroidectomy and 28 central lymph node dissection, being in 20 prophylactic. DNA was extracted from neoplastic cells and BRAF mutation was detected by PCR and sequencing. Analysis included age, preoperatively TSH, tumour size, multifocality, extrathyroidal extension (EET), LNMs, histological subtype, clinical stage and ultrasound features.

Results
The prevalence of the BRAF mutation (BRAF+) in our patients was 51.6%; 48.4% were negative (BRAF−). According to sex, 57% males and 45% females were BRAF+ (P = 0.68). Mean age was 46.8 years in BRAF+ vs 55.4 in BRAF− (P = 0.28); mean tumour size was 17.8 mm in BRAF+ vs 22.8 in BRAF− (P = 0.35). Multifocality was present in 66.6% of BRAF− and 50% of BRAF+ (P = 0.47). EET was found in 33% of BRAF− vs 56.2% of BRAF+ (P = 0.28). In 69% of BRAF+, classic variant of PTC was diagnosed, whereas 6% corresponded to follicular variant (P = 0.07). Mean TSH level was 3.97 mU/l in BRAF+ vs 2.17 in BRAF− (P = 0.35). The rate of central LNMs in patients undergoing PLNCD, was higher in BRAF+ than in BRAF− (63.6 vs 33%) (P = 0.37). Thyroglobulin level before thyroid RAI ablation was 5.65 ng/ml in BRAF+ vs 3 ng/ml in BRAF− (P = 0.9).

Conclusions
We did not find any significant association between BRAF+ and clinical and pathological features, not even with the presence of LNMs, probably due to the small size of the sample. Nevertheless, considering the high prevalence of occult LNMs in patients harboring BRAF mutation, preoperative analyses of BRAF could possibly be helpful to decide initial surgery in patients affected of PTC, as it has been suggested previously.

P1127

A case of papillary thyroid carcinoma in a patient with familial adenomatous polyposis of the colon
Aitzol Lizarraga Zafiaurre, Miguel Paja Fano, Aitziber Ugalde olano, Estibaliz Ugarte Abasolo & Natalia Covadonga Iglesias Hernandez Hospital of Basurto, Bilbao, Bizkaia, Spain.

Thyroid carcinoma is a rare extraintestinal manifestation of colonic familial adenomatous polyposis (FAP). This syndrome is caused by germline mutations in adenomatous polyposis coli (APC) gene, on chromosome 5q21-22. Many patients manifest various extracolonic features: upper gastrointestinal adenomas, congenital hypertrophic retinal pigment epithelial lesions, desmoids tumors, and
Metastatic papillary thyroid carcinoma arising from thyroglossal duct cyst

Metin Arslan¹, Ethem Turgay Ceri¹, Ozlem Turhan Iyidir¹, Cigdem Ozkan¹, Ceyla Konca Degertekin¹, Isilay Kalan¹, Alev Altinova¹, Majide Akturk¹, Fusun Balos Toruner¹, Goksun Ayvaz¹, Nuri Cakir¹ & Ferit Taneri²

¹Department of Endocrinology and Metabolism, Gazi University, Ankara, Turkey; ²Department of General Surgery, Gazi University, Ankara, Turkey.

The incidence of thyroid papillary carcinoma in thyroglossal duct cyst is <1%. Regional lymph node metastasis is usually seen in cases who have intra-thyroidal tumor. We report a case of thyroid papillary carcinoma arising from thyroglossal duct cyst with lateral lymph node metastasis who has a normal thyroid gland and benign central compartment lymph nodes.

Case report
A 38-year-old male patient was admitted with the complaint of swallowing in the neck. It was a cystic lesion (thyroglossal duct cyst?) and 16 mm in size on ultrasonography. The thyroid gland ultrasound was normal. There was a lesion on the left neck extending up from the upper to the lower jugular chain, measured 55 x 25 mm in size, containing millimetric calcifications which was suspected to be metastasis of papillary thyroid carcinoma. The fine needle aspiration cytology of this lesion was positive for metastases of papillary carcinoma of the thyroid. Thus, thyroglossal duct cyst excision and bilateral total thyroidec-tomy with central and left neck dissection was performed. Thyroglossal duct cyst specimen pathology has been reported as an invasion of central and left neck dissection which is 7 cm in diameter.

Conclusion
This is a rare case due to have a thyroid papillary carcinoma arising from thyroglossal duct cyst with lateral lymph node metastasis and without a tumor in thyroid gland and without central lymph node metastasis. As a result, while evaluating a thyroglossal duct cyst, in all cases, a detailed neck ultrasonography should be performed and biopsy should be done from suspected lymph nodes before planning the surgery.

DOI: 10.1530/endoabs.32.P1128
P1131  
Well differentiated thyroid-type carcinoma arising from struma ovarii: a report of two cases  
Jerome Barrera, Frances Lina Lantion-Ang & Leslie Quiva  
Philippine General Hospital, Manila, Metro Manila, The Philippines.

We report two cases of well differentiated thyroid-type carcinoma arising from struma ovarii managed in our institution.  
Case 1  
A 41-year-old female admitted due to abdominal pain and vomiting. Her abdomen was globular with palpable vague mass on lower abdomen. Ultrasound scan revealed 12.5×12.1×8.3 cm heterogenous mass with ascites. Total abdominal hysterectomy with bilateral salpingo-oophorectomy was done and histopathology results revealed papillary thyroid-type carcinoma arising from struma ovarii. Total thyroidectomy, radioactive iodine ablation and thyroxine suppression therapy were done. On follow-up there was no evidence of persistent tumor or recurrences.

Case 2  
A case of a 38-year-old, G3P2, female diagnosed with 16×15×12 cm cystic ovarian mass during the second trimester of her third pregnancy, underwent right salpingo-oophorectomy due to persistent abdominal pain. Histopathology revealed follicular carcinoma of thyroid type with no metastases. Further treatment of the malignancy was delayed due to current pregnancy. Patient delivered a healthy appropriate for gestational age baby boy via a spontaneous vaginal delivery. She is now scheduled to undergo thyroidectomy, radioactive ablation and thyroxine suppressive therapy. Due to the rarity of the disease, protracted clinical course and lack of uniform histological criteria for malignancy, diagnosis and management are still not universally accepted. Recent recommendations showed that well differentiated thyroid-type carcinoma arising from stuma ovarii as presented in our two cases should be diagnosed and managed as primary well differentiated carcinoma of thyroid gland.

DOI: 10.1530/endoabs.32.P1131

P1132  
Male patient with neck mass: ectopic cancer vs metastasis disease  
Coromoto Palermo1, Oberto Torres1, Jose Hernan Martinez2, Frieda Silva3-4, Madeleine Gutierrez3, Eva Gonzalez3 & Maria de Lourdes Miranda3  
1San Juan City Hospital, San Juan, Puerto Rico; 2Nuclear Medicine Department, School of Medicine UPR, San Juan, Puerto Rico.

Case of 33 years old male patient with an unremarkable past medical history, who after a car accident, a cystic nodular right neck mass was incidentally found by MRI of cervical spine. Physical examination revealed a mild tender right neck mass. He was clinically and biochemically euthyroid. Denied history of neck irradiation. No family history of thyroid disease or thyroid cancer. Excisional biopsy of right neck mass showed metastatic well differentiated papillary carcinoma of thyroid gland at lymph node. Total thyroidectomy with right modified neck dissection was performed. Histopathological report disclosed no evidence of malignant tumor within the thyroid gland (papillary cancer) as well as 16 right lymph nodes obtained from surgery. One month after surgery, thyroglobulin levels were elevated, 133.61 ng/ml (nv: 5–25 ng/ml) with negative anti-thyroglobulin antibodies (thyroglobulin antibodies: 11.8 μL/ml nv: 0–4.11). Thyroid scan and whole-body scan showed evidence of functional thyroid tissue remnants; this appears to be a right thyroid lobe. Also, a faint visualization of a right thyroid lobe. Antithyroid treatment given for 4 months with PTU 3×200 mg and propranolol 4×40 mg did not improve thyrotoxicosis therefore relevant surgical operation was taken into consideration. Although the patient was given PTU 3×200 mg, lithium 3×400 mg (pre-operatively for 1 month), lugol solution 3×5 drops (pre-operatively for 10 days), predol 3×20 mg (pre-operatively for 5 days) orally for pre-operative preparation, the patient’s status of thyrotoxicosis persisted and she was operated in spite of the existing risk. During and after the operation, no complications were encountered and the patient’s pathology result was found to be consistent the background of diffuse inflammation with areas of papillary thyroid carcinoma.

Conclusions  
This is an interesting case that manifests a highly resistant course and has a coexistence of hyperthyroidism and thyroid cancer.

DOI: 10.1530/endoabs.32.P1132

P1133  
Papillary carcinoma with diffuse toxic goiter and highly resistant course  
Gulcin Cengiz Ecemis1, Selahattin Saykil2, Hacer Salman3 & Nurten Bozlak4  
1Dr I Sevki Atasagun Atasagun Hospital Clinic of Endocrinology, Nevsehir, Turkey; 2Dr I Sevki Atasagun Atasagun Hospital Clinic of General Surgery, Nevsehir, Turkey; 3Dr I Sevki Atasagun Atasagun Hospital Clinic of Internal Medicine, Nevsehir, Turkey; 4Dr I Sevki Atasagun Atasagun Hospital Clinic of Pathology, Nevsehir, Turkey.

Introduction  
The coexistence of hyperthyroidism and thyroid cancer is considered a rare event. We describe a case of papillary carcinoma of the thyroid that mimicked a diffuse toxic goiter.  
Case report  
A 26-year-old female patient presented with a complaint of malaise was diagnosed to have thyrotoxicosis and following the tests performed (sT3: 7.7 (1.7–3.7 ng/dl), sT4: 2.5 (0.7–1.49 ng/dl) TSH: <0.0025 (0.35–4.94 μU/ml)). Patient was clinically stable; without any palpitation, sweating, weight loss or ophthalmopathy. Thyroid was palpable and graded 1b according the Physical examination. Ultrasonographic findings were as follows: both lobes were heterogeneous, hypoechoic lobulated and no nodule was identified. Scintigraphic evaluation was not performed due to a problem at thyroid scintigraphy device. Anti-thyroglobulin antibody, anti-TPO antibody and TSH receptor antibody were found to be negative. The patient was initially started on methimazole and due to development of rash she was then switched to propylthiouracil (PTU). Antithyroid treatment given for 4 months with PTU 3×200 mg and propranolol 4×40 mg did not improve thyrotoxicosis therefore relevant surgical operation was taken into consideration. Although the patient was given PTU 3×200 mg, lithium 3×400 mg (pre-operatively for 1 month), lugol solution 3×5 drops (pre-operatively for 10 days), predol 3×20 mg (pre-operatively for 5 days) orally for pre-operative preparation, the patient’s status of thyrotoxicosis persisted and she was operated in spite of the existing risk. During and after the operation, no complications were encountered and the patient’s pathology result was found to be consistent the background of diffuse inflammation with areas of papillary thyroid carcinoma.

Conclusions  
This is an interesting case that manifests a highly resistant course and has a coexistence of hyperthyroidism and thyroid cancer.

DOI: 10.1530/endoabs.32.P1133

P1134  
Brain metastases of papillary thyroid cancer: a case report and literature review  
Leila Ahmed-Ali & Farida Chentli  
Department of Endocrinology and Metabolic Diseases, Bab El Oued Hospital, Algiers, Algeria.

Introduction  
Papillary thyroid carcinoma is characterized by a good prognosis and a slow progression. Its metastases are usually located in cervical lymph nodes. But, sometimes they can reach the lung and bones. Cerebral metastases are exceptional as they have been reported in only 4%. Single or multiple, they can be totally symptomatic, but they are life threatening and require specific care as in the following case.

Case report  
A man aged 56, was referred to our unit for vertebral metastasis whose biopsy argued for thyroid origin. Histological examination of the thyroid confirmed the papillary form which was classified as T3N0M1. He previously underwent radiotherapy for compression of the spinal cord. Radiological explorations demonstrated lung and bone metastases. Thyroglobulin rates were very high (>600 ng/ml). Just before radio iodine intake, he suddenly suffered from vomiting and headaches evocating increased intracranial pressure. Brain CT scan showed multiple brain lesions with hydrocephaly needing a ventricular shunt. Unfortunately just before being operated on, he died from severe cerebral haemorrhage.

Conclusion  
Brain metastases are very rare in papillary thyroid carcinoma. They are usually seen in the late stage of the disease as in our case. An early detection and a specific treatment can probably improve the quality of life and avoid brain hypertension and cerebral haemorrhage.

DOI: 10.1530/endoabs.32.P1134

Endocrine Abstracts (2013) Vol 32
P1135
Choroidal bilateral metastases from thyroid carcinoma: a report of a case and review of the literature
Leila Ahmed-Ali, Lylia Amirou & Farida Chentli
Department of Endocrinology and Metabolic Diseases, Bab El Oued Hospital, Algiers, Algeria.

Introduction
Metastases of thyroid carcinoma to the choroid and/or orbit are rare and usually occur at an advanced stage of the disease. The principal symptoms are decreased or blurred vision and/or persistent eye pain but they can be totally asymptomatic.

Observation
MH 58-year-old woman treated for thyroid carcinoma with multiple secondary metastases (lung, bone, adrenal, and liver). Biopsy of a pulmonary localization was in favor of a primitive thyroid origin. Ophthalmological examination after a bone localization in the roof of the orbit showed painless palpable mass in the left orbital arch, reduced vision of the right eye. Angiography, ultrasound b, and OCT were in favor of bilateral choroidal metastases.

Conclusion
Choroidal metastases of thyroid carcinomas are rare and occur in the context of metastatic seeding. The diagnosis is made through non-invasive imaging methods. The therapeutic management is difficult because secondary lesions of thyroid origin are resistant to chemotherapy and radiotherapy.

DOI: 10.1530/endoabs.32.P1135

P1136
Thyroglobulin measurement in fine needle aspirates from cervical lymph nodes
Cristina Ribeiro1, Sandra Paiva1, Miguel Melo1, Sofia Gouveia1, Fatima Leitão2 & Francisco Carrilho1
1Endocrinology, Diabetes and Metabolism Department, Coimbra’s University Hospital, Coimbra, Portugal, 2Clinical Pathology Department, Coimbra’s University Hospital, Coimbra, Portugal.

Introduction
Thyroglobulin (TG) measurement in fine needle aspirates cytology (FNAC) needle washout has become an important method for diagnostic of cervical lymph nodes, particularly in patients with differentiated thyroid cancers, but also in some patients before the diagnostic. We report some clinical cases to confirm its importance in these situations.

Patients and methods
In our department we use this method since 2007. We report seven patients with thyroid disease referred to our department. The ultrasound examination revealed the presence of suspicious cervical lymph nodes. FNAC was performed in the thyroid nodules. The lymph nodes were punctured for cytology, together with the TG in the needle washout in the last.

Results
From the patients with high TG, four were already submitted to thyroidectomy, confirming the diagnostic of papillary cancer. Patient 5 has TG antibody elevated, which can contribute to the low level of TG.

<table>
<thead>
<tr>
<th>Pts</th>
<th>Lymph node cytology</th>
<th>TG (nMoI)</th>
<th>Nodule cytology</th>
<th>Gender</th>
<th>Age</th>
<th>Previous cytology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Th. tumour?</td>
<td>24 857</td>
<td>Insufficient</td>
<td>Female</td>
<td>65</td>
<td>Insufficient</td>
</tr>
<tr>
<td>2</td>
<td>Insufficient</td>
<td>250 219</td>
<td>Papillary</td>
<td>Female</td>
<td>36</td>
<td>Colloid</td>
</tr>
<tr>
<td>3</td>
<td>Insufficient</td>
<td>15 999</td>
<td>Colloid</td>
<td>Female</td>
<td>43</td>
<td>Colloid</td>
</tr>
<tr>
<td>4</td>
<td>Insufficient</td>
<td>12 209</td>
<td>Colloid</td>
<td>Female</td>
<td>34</td>
<td>Colloid</td>
</tr>
<tr>
<td>5</td>
<td>Papillary m</td>
<td>48</td>
<td>–</td>
<td>Male</td>
<td>19</td>
<td>Insufficient</td>
</tr>
<tr>
<td>6</td>
<td>Lymphoma</td>
<td>&lt;0.2</td>
<td>Insufficient</td>
<td>Male</td>
<td>36</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>Lymphoma m</td>
<td>&lt;0.2</td>
<td>–</td>
<td>Male</td>
<td>28</td>
<td>–</td>
</tr>
</tbody>
</table>

Conclusion
In these patients, TG in the needle washout in FNAC proved to be a good contribution to the diagnostic of malignancy, making its treatment faster and more efficient. The role of this method is particularly relevant due to the high rate of ‘insufficiency’ in the cytology of lymph nodes (cystic).

DOI: 10.1530/endoabs.32.P1136

P1137
Poorly differentiated thyroid carcinoma: a clinicopathologic study of 30 cases
Fella Hasbellaoui1, Nabilah Meziani1, Anissa Khelifa1, Khadijda Ziani1, Samia Amokrane2, Fatima Zohra Benesera1, W. Mehkouk1, M. Boudassa1, S Hadjarab1, D Fouidi1, N Kesri1, L Griene3, M Aftane2, L Amokrane & Mourad Senrouni1
1Endocrinology and Nuclear Medicine Department, Centre pierre et Marie Curie, Algiers, Algeria; 2Pathology Department, Uni Mustapha Bacha, Algiers, Algeria; 3Biochemistry Department, CPMC, Algiers, Algeria; 4Radiotherapy Department, CPMC, Algiers, Algeria.

Introduction
Poorly differentiated thyroid carcinoma are considered as a link between well differentiated carcinoma and undifferentiated ones. The histological definition is still controversial and various criteria have been proposed.

Objective
The main objective of this study is to assess the management of poorly differentiated thyroid cancer in our department.

Materials and methods
We reported 30 patients with poorly differentiated carcinoma diagnosed during the period of 5 (05) years (2008–2012).

We analysed the management of these patients. There were classified in age, sex, clinical outcome, initial distant metastasis, treatment (surgery, radiotherapy, and chemotherapy) and evolution.

Results
A 30 patients diagnosed between January 2008 and December 2012. Female in majority. Middle age 45 years (25–72), 75% with distant metastasis at diagnosis (brain, bone and pulmonary).

Surgery was the first treatment proposed: total thyroidectomy practiced in 60%; in other cases partial thyroidectomy or biopsy due to local tumor invasion. Radiiodine therapy was indicated after surgery, not possible to be done in 10 patients because of aggressiveness.

Radiotherapy or external beam irradiation when incomplete surgery. Chemotherapy done for two patients.

Evolution: death was reported in seven patients, stabilization performed in ten patients even with distant metastasis. Disease progression in 13 patients.

Discussion
Poorly differentiated thyroid cancers are defined as follicular neoplasm with intermediate position. There was The Turin proposal (2006): the first criteria were solid, trabecular or insular growth, they add presence of necrosis, high mitotic index and nuclear features.

The histology is the first difficulty of this entity. The aggressiveness of this pattern need an early management and treatment. surgery and radio iodine therapy seem to give the best results when possible. Other treatment are done when disease progression with distant metastasis.

The prognosis of this entity is very bad especially when distant metastasis are at diagnosis.

DOI: 10.1530/endoabs.32.P1137

P1138
Adrenal metastases from thyroid cancers
Mohammed Bendali, Faiza Boutekedjiret, Assila Lylia Amirou & Farida Chentli
Department of Endocrine and Metabolic Diseases, Bab Oued Hospital, Algiers, Algeria.

Introduction
Adrenal metastases due to thyroid cancers deemed to very rare as adrenal glands are not a common site of metastases from thyroid cancer. When the phenomenon occurs the prognosis is very poor as adrenal metastases usually do not fix radioactive iodine. Our aim is to report three cases.

Case reports
No. 1: a woman aged 57 harbouring anaplastic thyroid carcinoma classified T4, N1, M6, consulted for back pain, severe fatigue and skin pigmentation. Abdomen ultrasound showed very large tumours in both adrenals. Hormonal assessment demonstrated low cortisol with high ACTH. Although she was taking glucocorticoids at high dose, she died 1 month later after an adrenal crisis.

No. 2: a woman aged 56 was referred for oncocytic papillary carcinoma with pulmonary and bone metastases. Checking for other sites showed liver and adrenal localizations. Fine needle aspiration of large adrenal masses confirmed the thyroid origin. More than 1 year later she is still alive, but with a large diffusion of the disease.

Endocrine Abstracts (2013) Vol 32
No. 3: a 53-year-old woman was sent for a suspect thyroid tumour. Body scan showed pulmonary, lymph nodes and bones metastases. After surgery the papillary thyroid cancer was confirmed. Some months later a right adrenal mass was discovered. She died 2 years later.

Conclusion
The 3 three women aged 53–57 have adrenal metastases from thyroid cancers. It was an anaplastic form in one case, and a papillary aggressive form in two other cases. Life duration varies from 1 month to 2 years after the adrenal metastases were diagnosed. Endocrinologist should check systematically for those metastases and treat them if they are at an early stage, if not the prognosis is poor as in our cases.

DOI: 10.1530/endoabs.32.P1138

P1139
Thyroid papillary carcinoma in a toxic adenoma: case report
Raquel G Martins1,2, Joana Couto1, Ana Paula Santos3, Maria João Matos3, Rosa Capelo1, José Pedro Silva1, Inês Lucena1, Mariana Cambão1 & Isabel Torres1
1Portuguese Institute of Oncology, Oporto, Portugal; 2School of Medicine, University of Oporto, Oporto, Portugal; 3São João Hospital, Oporto, Portugal.

Introduction
Malignant toxic thyroid nodules are rare, with few cases described in the literature. The prevalence of malignancy in toxic adenomas varies between 1 and 8% in different series (most, corresponding to <2.5%). For that reason, international guidelines recommend that they should not be submitted to fine needle aspiration biopsy.

Case report
A 42-year-old female patient without relevant previous medical history was admitted to our hospital because of two thyroid nodules (37 e 13 mm) in the left lobe (without adenopathies); analytically, she had subclinic hyperthyroidism. Fine needle aspiration biopsy diagnosis was colloid nodular hyperplasia;131I scan showed tracer activity in a left nodule with suppression of extranodular tissue. Thyroid hormone measurements were repeated and were compatible with clinical hyperthyroidism. She was initially treated with methimazole and then submitted to left hemithyroidectomy which showed a thyroid papillary carcinoma (folicular variant) in both nodules associated with a lymph node metastasis. She was finally submitted to total thyroidectomy (remaining tissue didn’t present neoplastic involvement) and 131I ablative treatment and remains under surveillance with levothyroxine suppressive therapy.

Conclusions
The authors describe a rare association of hot nodules and papillary thyroid carcinoma, with a nondiagnostic cytology, stressing the importance of long-term surveillance of toxic nodules that underwent nonsurgical therapies. Published cases of differentiated thyroid carcinoma appearing in hot nodules seem to suggest a similar prognosis to that present in nontoxic nodules.

DOI: 10.1530/endoabs.32.P1139

P1140
Ultrasonographic signs suggestive of malignancy in thyroid nodules
Inmaculada González Molero, Rosario Vallejo-Mora, Marta Dominguez López, Stella González Romero, Francisca García Torres, Marisol Ruiz de Adana & Federico Soriguer Carlos Haya Hospital, Málaga, Spain.

Introduction
Thyroid ultrasound is a widely used tool in monitoring thyroid nodule, allowing us to assess the size and other sonographic signs suspicious of malignancy, facilitating decisions about diagnosis and treatment.

Objectives
To evaluate the presence of ultrasonographic signs suggestive of malignancy in patients with thyroid carcinoma in our hospital.

Material and methods
Retrospective study of 63 patients with thyroid carcinoma in our hospital (2009–2011). We analyzed: age, sex, sonographic features (ECO held during the year before surgery) and pathological definitive diagnosis.

Results
We analyzed 63 patients, 54 were women (83.1%) with mean age of 49.23 ± 15.48 years. The final pathologic diagnosis was: papillary thyroid carcinoma: 84.6%, follicular thyroid carcinoma: 10.8%, medullary carcinoma: 1.5% and others 3.1%.

Previous ultrasound data
41 (63.1%) were single nodule, the rest were multinodular thyroid goiter. The average size of the nodule was 27.6 ± 16.5 mm. 50 nodules (76.9%), were solid, the rest were solid-cystic. Hypoechogeticity was reported in 19 (30.6%) (no record of echogenicity 58%), calcifications in 13 (20.6%), central intranodular vascularization in 10 (15.9%), irregular margins in 5 (7.7%) peripheral halo formation in 9 (14.3%) and presence of regional lymphadenopathy in 9 (15%). With respect to volume, three-dimensional sonographic size was reported in 29.5%, two in 26.2% and only one in 44.3%.

We detected at least one ultrasound data suggestive of malignancy in 42.8%, two in 31.7%, three in 11.1% and four in 7.9%. These data were not detected in 6.3% (4 patients).

Conclusion
Our results confirm that thyroid ultrasound can help in the management of thyroid carcinoma because most patients had any signs of malignancy.

DOI: 10.1530/endoabs.32.P1140
Yilmaz, O P386
Yin, L P724
Ylli, A P782
Yoldi, A P233 & P714
Yoleri, O P304
Yon, L P560
Yonem, O P151
Yoo, HJ P762
Yoon, J P58
Yosu, A P1054
Younas, A P337
Young, J OC5.6, P637, P649 & S12.1
Young, W P862
Yu, SH P376, P742 & P762
Yuan, L P302
Yudina, A P704
Yuksel, E P62
Yunilainen, O P685
Yusof, BNM P206
Yusoff, Y P206
Yuvanc, HO P386
Zabalos, F P941
Zabransky, M P630
Zabullene, L P140, P425 & P574
Zabulis, V P425
Zacharieva, S P846 & S21.2
Zacharin, M P846
Zafon, C P993
Zaghrouane, H P628
Zagrebaeva, O P814
Zainudin, S P206
Zajac-Marczewska, M P244
Zak, P P1042
Zakharova, N P615
Zaleskaya, O P765
Zambo, K P1097
Zambonin, L P1099
Zamorano, NF P54
Zampetti, B P67
Zanon-Moreno, V P179
Zane, M P1099
Zanetti, MLI P472
Zaouali, M P628
Zapanti, E P1038
Zareinejad, M P116
Zarkovic, M P1051, P290, P57, P620 & P985
Zatelli, MC P519, P539, P540, P549 & P6
Zavattaro, M P467 & P473
Zavoral, M P1076 & P551
Zaydieva, Y P612
Zdunowski, P P925
Zeller, C S11.3
Zekenuova, K P412 & P787
Zelaya, RV P444 & P448
Zelinkova, Z P660
Zelissen, P P49
Zellagui, H P261
Zemdegs, J P746
Zengin, A P686 & P741
Zengin, K P759
Zervou, M P26
Zetterberg, H P703
Zezem, S P1093
Zeyda, M P728
Zgliczynski, W P925
Zhao, S P350
Zhao, X P591
Zheng, SF P971
Zhukouskaya, VV P74
Zhiravlyova, L P407, P423 & P424
Zhyzhneuskaya, S P550
Ziani, K P1137
Ziegglansberger, W P858
Zieleniewski, W P216
Zielinski, GP895 & P924
Ziora, K P795
Zirilli, L P881
Zitzmann, M P652
Zochowska, E P567
Zohra Benserai, F P1137
Zolfaghari, Z P596
Zoli, M P850
Zorić, S P761
Zosin, I P1018, P177 & P914
Zouli, C P1035
Zubelewicz-Szkodzinska, B P191
Zubillaga, I P68 & P777
Zucchi, R P744 & P991
Zueger, T P180 & P886
Zulaurre, AF P1127
Zuhur, SS P111
Zulewski, H P215