Endocrine Abstracts

November 2019 Volume 65
ISSN 1479-6848 (online)

Society for Endocrinology BES 2019

11–13 November 2019, Brighton

published by
bioscientifica

Online version available at
www.endocrine-abstracts.org

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Volume 65
November 2019

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Plenary Lectures

Clinical Endocrinology Trust Lecture

PL1

Controlling cortisol in cardiometabolic disease

Brian Walker[1,2]

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In both spontaneous and iatrogenic Cushing's syndrome, chronic glucocorticoid excess causes obesity, hyperglycaemia, hypertension and accelerated cardiovascular disease. We have pursued the global hypothesis that elevation of cortisol causes cardiovascular disease in the general population, and that the underlying mechanisms will reveal new therapies for cardiometabolic diseases. Circumstantial support is provided by cohort studies, in which higher plasma cortisol is associated with cardiovascular risk factors and is predictive of subsequent cardiovascular disease. To test causality, however, requires either intervention studies or identification of genetic determinants of cortisol. To explore genetic variants associated with cortisol we established the CORtisol NETwork (CORNET) consortium. Using the relatively crude but widely available and heritable trait of morning plasma cortisol the most recent CORNET genome wide association meta-analysis of >7 M SNPs in nearly 25 000 people has identified only one influential locus, spanning the *SERPINA6* and *SERPINA1* genes which encode for corticosteroid binding globulin (CBG) and alpha1-antitrypsin (AAT), respectively. Mendelian randomisation analysis reveals that cortisol-associated SNPs are also associated with cardiovascular disease (in UK Biobank and CARDIOGRAMplusC4D), providing evidence that elevated cortisol is causative for cardiovascular disease. Identifying genetic variants which influence cortisol has also provided insights into cortisol biology. Recent eQTL analysis in 7 tissues from 600 subjects has shown that SNPs in *SERPINA6* which predict higher cortisol are associated not only with increased CBG expression in liver but also with networks of altered glucocorticoid-regulated gene expression in adipose tissue. This indicates that CBG influences the delivery of cortisol to peripheral tissues. One mechanism for this may involve cleavage of CBG by neutrophil elastase within adipose tissue, a process which is inhibited by AAT. Targeting these pathways may yet provide new approaches that can be tested in intervention studies to prevent cardiometabolic disease.

DOI: 10.1530/endoabs.65.PL1

Society for Endocrinology Starling Medal Lecture

PL2

From its origins to the modern metabolic network

Markus Ralser[1,2]

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Life runs on many thousands of different chemical reactions, known collectively as cell metabolism. Metabolic reactions are vital for keeping cells and organisms growing and alive, and problems with cellular metabolism are implicated in ageing and diseases such as cancer, diabetes and brain disorders. Rather than thinking about cell metabolism as a collection of individual reactions, we are working to understand metabolism as a dynamic, interconnected network of processes that adapts in response to changes and stresses in the environment, and that evolves and functions as an entity. In the Starling Medal lecture, I'll summarize our efforts in using yeast as a simple system for conducting hundreds to thousands of analytical measurements, allowing us to study how these complex metabolic processes are controlled, and how they are reconfigured in response to environmental changes. By taking detailed precision measurements of the genes and molecules involved in metabolic processes and putting the data into computer analysis programmes, we can see how the cell's metabolism adapts and changes in response to various stresses and strains. And we can also see what happens when crucial parts of the system are altered or faulty, as a model for human diseases, as well as derive the very basic principles of metabolism, like the ones that enabled its origin in early evolution.

DOI: 10.1530/endoabs.65.PL2

Society for Endocrinology Dale Medal Lecture

PL3

From Carney complex to gigantism and Cushing disease: an insight into the genetics of pituitary tumors

Constantine Stratakis

Section on Endocrinology and Genetics (SEGEN), Eunice Kennedy Shrive National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH), Bethesda, Maryland, USA

In the last 30 years, an unprecedented production of new knowledge about the tumors of the pituitary gland has led to a series of new discoveries important for the understanding of how these neoplasms form and the management of our patients. These tumors are often caused by germline or somatic mutations in an ever expanding list of genes; a growing list of genetic defects associated with inherited predisposition to pituitary tumors means implications for the families of the patients, too. We present some of the newest data on PRKAR1A (Carney complex), AIP (FIPA), Menin (MEN1), succinate dehydrogenase (SDH-3PAS), GPR101 (XLAG) and other defects causing pituitary adenomas, including unpublished data on the genetics of Cushing disease that we have obtained recently in our laboratory at the US-based National Institutes of Health.

DOI: 10.1530/endoabs.65.PL3

Society for Endocrinology Transatlantic Medal Lecture

PL4

How is alkaline phosphatase essential for bone? The transatlantic stories

Michael P Whyte[1,2]

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Alkaline phosphatase (ALP) was discovered by Robert Robison, PhD in London in 1923. In New York in 1932, he added to his hypothesis that ALP functioned in skeletal calcification by liberating inorganic phosphate (Pi) for hydroxyapatite crystal formation, perhaps from a hexosephosphoric ester, some unknown factor also conditioning this process. In 1948 in Toronto, Canada, 'hypophosphatasia' (HPP) was coined by John C. Rathbun, MD to describe a unique rickets without reductions in circulating calcium or Pi levels and seemingly paradoxically low serum ALP activity. HPP would become the dento-osseous disease that features tooth loss and rickets in childhood and osteomalacia in adult life due to deficiency of the "tissue nonspecific" (bone/liver/kidney) isoenzyme of ALP (TNSALP). In the 1960s, Graham Russell, PhD in Leeds and Herbert Fleisch, PhD in Davos, Switzerland found inorganic pyrophosphate (PPi) levels were elevated in the blood and urine of patients with HPP. Robison's 'unknown' would prove to be this ALP natural substrate and inhibitor of biomineralization. In 1985, we discovered elevated plasma levels of pyridoxal 5′-phosphate in HPP revealing that TNSALP is a cell-surface enzyme. In 1988, HPP became the inborn-error-of-metabolism featuring TNSALP deficiency upon discovery in Philadelphia, USA that a boy in Halifax, Canada with lethal HPP harbored a homozygous loss-of-function missense mutation within the 'candidate' ALPL gene that encodes TNSALP. HPP as an "experiment-of-nature" awakened interest in the bisphosphonates, synthesized by European chemists decades earlier, for their potential to improve some skeletal diseases as their P-C-P core rather than the P-O-P core of PPi resisted hydrolysis by TNSALP. In 2015, multinational approval of asfotase alfa, pioneered in Montreal, Canada as a TNSALP-replacement therapy for HPP, would decrease endogenous PPi levels and restore 'hard tissue' mineralization. The first clinical trial began with an infant flown from Belfast, Northern Ireland to Winnipeg, Canada. How ALP is essential for bone has been a transatlantic story.

DOI: 10.1530/endoabs.65.PL4

Society for Endocrinology International Medal Lecture

PL5

The melanocortin microcircuitry and its role in energy homeostasis

Roger Cone, Patrick Sweeney, Luis Gimenez & Ciria Hernandez

University of Michigan, Ann Arbor, Michigan, USA

The central melanocortin circuitry is at the heart of the adipostat, and functions as a bidirectional switch on the control of energy storage. The circuitry is composed of the anorexigenic arcuate POMC neurons, and the orexigenic arcuate AgRP neurons, and their melanocortin-3 (MC3R) and melanocortin-4 (MC4R) target neurons, found in key neuroendocrine, behavioral, and autonomic control sites throughout the brain. Mutations in the MC4R, present at a composite allele frequency as high as 1 in 1500, are the most common cause of human syndromic obesity. The MC4R is a well validated target for the treatment of syndromic obesity, but a lack of understanding of the structure and function of the receptor have hindered the development of MC4R agonists for the treatment of common dietary obesity. New data on the molecular structure and signaling of the MC4R will be presented here that may aid in the development of next generation MC4R therapeutics. Understanding of the role of the MC3R has been slower to develop. Recently, we demonstrated that the MC3R is expressed presynaptically on AgRP neurons, regulates GABA release from these cells, and is required for control of the boundary conditions of energy homeostasis. We now demonstrate the mechanistic utility of stimulation or inhibition of MC3R neurons using both genetic and pharmacological tools.

DOI: 10.1530/endoabs.65.PL5

Society for Endocrinology European Medal Lecture

PL6

Mechanisms and consequences of endocrine autonomy – lessons learned from the adrenal cortex

Felix Beuschlein

UniversitätsSpital Zürich, Zurich, Switzerland. Klinikum der Universität München, Munich, Germany

The advent of new genetic techniques that allow for high-throughput sequencing in surgical tumour tissues and germline DNA has boosted progress in many fields of biomedical research. The technique has been proven to be particularly fruitful in the area of endocrine tumours with many new driver genes being identified over the last few years that are involved in cell growth but more importantly in hormonal autonomy. For the adrenal gland examples account for aldosterone and cortisol producing adrenal adenomas, adrenocortical carcinomas as well as pheochromocytomas. In succession with these insights in genetic contributors in adrenal pathophysiology, deep clinical and biochemical phenotyping has allowed for genotype/phenotype correlations that provide the starting point for improved mechanistic insights. These studies further provide the basis for the implementation of novel diagnostic concepts that make usage of hormonal pattern that derived from the tumors and metabolomic fingerprints that reflect target tissue responses. As to be expected, adjustment of clinical management in patients with adrenal tumours that would rely solely or in great part on genetic information is lacking behind. The presentation will provide an update on the current state of the art in personalized approaches and the yet achieved spectrum of precision medicine for adrenal tumour patients.

DOI: 10.1530/endoabs.65.PL6

British Thyroid Association Pitt-Rivers Lecture

PL7

Thyroid cancer genomics, differentiation state and response to radioiodine

James Fagin

Memorial Sloan Kettering Cancer Center, New York, USA

The use of RAI for remnant ablation, as adjuvant therapy or as treatment for recurrent or metastatic disease is undergoing a significant reappraisal, based on its questionable efficacy in various disease contexts. Until recently postoperative RAI treatment was given to all patients with thyroid cancer regardless of the pathological stage of the disease. Although its use for low risk forms of thyroid cancer has diminished, current indications for adjuvant RAI treatment are not based on randomized clinical trials, but instead on consensus expert recommendations that rely on retrospective studies, despite their methodological weaknesses and biases. Most thyroid cancers are driven by oncoproteins that activate MAPK signaling, and the transcriptional output of this pathway is inversely correlated with the expression of genes that govern many of the specialized functions of thyroid cells, including the ability to incorporate iodide into thyroid hormones. Most clinical guidelines recommend treating patients with tumors > 2 cm or with significant nodal disease with RAI after surgery. In our view this is problematic, as tumors giving rise to nodal disease are markedly enriched for $BRAF^{V600E}$, which have a high MAPK pathway flux and are mostly unresponsive to RAI. We will discuss the genomic determinants of the thyroid differentiation state in thyroid cancer, their relationship to RAI avidity and the extent by which thyroid differentiation can be restored by treatment with selective RAF or MEK inhibitors, or with combinations of compounds that block the MAPK output more profoundly. We will also discuss insights arising from the analysis of patients with exceptional responses to radioactive iodine, and by contrast, the genetic lesions that determine irreversible loss of thyroid identity.

DOI: 10.1530/endoabs.65.PL7

Clinical Endocrinology Trust Visiting Professor Lecture

PL8

Cushing's syndrome as a model of endocrine tumorigenesis

Jérôme Bertherat[1,2]

[1]Endocrinology Departement, Reference Center for Rare Adrenal Diseases, Cochin Hospital, Paris, France; [2]INSERM U1016, Paris University, Paris, France

Cushing's syndrome is a fascinating clinical challenge, both for diagnosis and management. Despite being a rare disease, it has many causes consisting of a broad variety of tumors. These tumors can arise from different tissues (i.e. pituitary, adrenal, lung…) varying from small benign and even non detectable tumors, to large aggressive cancers. The secretory spectrum of these tumors is broad qualitatively and quantitatively. It results from the molecular alterations that accumulate and participate in the tumor development, determining the differentiation of the tumor cells. This last decade, genomics led to spectacular progress in the identification of genetic and epigenetic alterations of many type of tumors causing Cushing's syndrome. This allows now to depict the landscape of the genetic and epigenetic alterations of these tumors. This help to understand the major determinants of the different tumors types, their secretory capacity and their growth. For instance benign adrenocortical tumors (adenomas or micronodular adrenal hyperplasia) due to germline or somatic defect of main component of the cAMP pathway (i.e. *PRKACA*, *PRKAR1A*…) are small benign tumors causing overt Cushing. Inactivating germline mutations of *ARMC5*, identified by a combined genomic approach in Primary Bilateral Macronodular Adrenal Hyperplasia (PBMAH), cause benign large multiple adrenocortical tumors, containing very few chromosomal alterations and responsible for moderate cortisol excess. Integrated genomics of adrenocortical cancer (ACC) identified recurrent multiple alterations in driver genes linked to different gene expression, chromosomal and methylation profiles. This molecular classification of ACC is strongly associated with tumor outcome, allowing new molecular tools for prognostication. Somating mutations of USP8 identified by exome analysis are observed in a specific sub-group of pituitary corticotroph tumors causing Cushing disease. The molecular classification resulting from genomics studies clearly help to better understand the heterogeneity of the various causes of Cushing' syndrome, supporting an individualized approach and new treatments.

DOI: 10.1530/endoabs.65.PL8

Society for Endocrinology Medal Lecture

PL9

Sex steroids and the endometrium: dynamics and disorders

Douglas Gibson, Frances Collins, Ioannis Simisidellis, Phoebe Kirkwood, Arantza Esnal-Zufiaurre & Philippa Saunders

The University of Edinburgh, Edinburgh, UK

The endometrium is a complex tissue with luminal and glandular epithelial cell layers supported on a multicellular stromal compartment; in women the inner (luminal) portion of the tissue breaks down and is shed during menstruation. The endometrium is exquisitely sensitive to the actions of sex steroids (oestrogens, progestogens and androgens) produced in ovarian and other extra gonadal tissues and delivered via blood vessels that rapidly develop and mature within the tissue

(endocrine system). Our own studies have recently highlighted a previously under-appreciated role for local (intracrine) pathways in fine-tuning tissue function to support implantation. We have used cell, tissue and animal models to explore the role of oestrogen and androgen receptors, and their natural ligands, in normal endometrial function and to determine how these are dysregulated in disorders including infertility, endometriosis and cancer. We have documented dynamic, spatial and temporal expression of both full-length (wild type) oestrogen receptors and ER splice variant isoforms during the normal cycle and identified changes in response to malignant transformation. We have shown oestrogens play a key role in regulating the function of immune cells that play an important role in preparation for implantation and in the formation and survival of extra-uterine endometriosis lesions. Studies using DHT and selective androgen receptor modulators (SARMs) have confirmed a role for androgen receptor mediated pathways in regulating stromal-epithelial cross talk. In summary, understanding the mechanisms regulated by sex steroid receptors in the endometrium provides the platform for improved medical therapies for endometrial disorders as well as novel insights into the impact of steroids on processes such as angiogenesis and tissue repair.

DOI: 10.1530/endoabs.65.PL9

Society for Endocrinology Jubilee Medal Lecture

PL10

Pituitary cells alive: hormone genes pulsing on and off

Julian Davis

University of Manchester, Manchester, UK

Technical advances frequently lead to surprises. Studies of gene expression have used reporter genes since the 1980s to assess how mammalian gene promoters are activated or repressed. Two of the most widely used reporters are firefly luciferase and green fluorescent protein, and both have the advantage that their expression can be seen, and their bioluminescence or fluorescence readily measured. In studying how hormone genes were controlled in the pituitary, we used quantitative microscopic imaging of cell lines transfected with either luciferase or destabilised EGFP linked to the human prolactin gene locus. We expected to find that gene expression varied in response to standard stimuli, but to our surprise discovered that gene expression was dramatically pulsatile, fluctuating from hour to hour. We used mathematical modelling to evaluate the pulses initially as if they were binary on-off events, and estimated the length of active and inactive periods. In order to study normal cells we created transgenic rats expressing prolactin-reporter genes in the anterior pituitary. This allowed us to look at the patterns of pulsing gene expression in normal pituitary cells in the context of intact tissue. We found that the characteristic timing of transcriptional pulses were not circadian, and changed during development through fetal, neonatal and adult life. It also became clear that gap junctional communication in a lactotroph cell network was necessary for coordination in the timing of transcriptional pulses between nearby cells. The discovery that gene transcription was pulsatile was unexpected, and means that the behaviour of living cells in real time is more complex than we had imagined from earlier biochemical investigations using cell extracts. Biological timing of many cellular processes, including gene transcription, is a vital aspect of our understanding different physiological and pathological states, and likely to underlie the resilience and adaptation of the endocrine system.

DOI: 10.1530/endoabs.65.PL10

Debate: Nature vs Nurture

This house believes nature not nurture determines our bodyweight

D1.1

Abstract unavailable

D1.2

Abstract unavailable

Society for Endocrinology Journal Awards

Society for Endocrinology Journal Award – *Journal of Endocrinology*

JA1

FGF21 acts as a negative regulator of bile acid synthesis

Michelle Chen, Clarence Hale, Shanaka Stanislaus, Jing Xu & Murielle Veniant

Journal of Endocrinology, 2018, **237**(2): 139–152 (DOI: https://doi.org/10.1530/JOE-17-0727)

DOI: 10.1530/endoabs.65.JA1

Society for Endocrinology Journal Award – *Journal of Molecular Endocrinology*

JA2

HDAC inhibitors impair Fshb subunit expression in murine gonadotrope cells

Gauthier Schang, Chirine Toufaily & Daniel J Bernard

Journal of Molecular Endocrinology, 2019, **62**(2): 67–78 (DOI: https://doi.org/10.1530/JME-18-0145)

DOI: 10.1530/endoabs.65.JA2

Society for Endocrinology Journal Award – *Endocrine-Related Cancer*

JA3

Notch pathway inhibition targets chemoresistant insulinoma cancer stem cells

Ylenia Capodanno, Floryne O Buishand, Lisa Pang, Jolle Kirpenstenijn, Jan Mol & David Argyle

Endocrine-Related Cancer, 2018, **25**(2): 131–144 (DOI: https://doi.org/10.1530/ERC-17-0415)

DOI: 10.1530/endoabs.65.JA3

Society for Endocrinology Journal Award – *Endocrine Connections*

JA4

GH deficiency in patients with spinal cord injury: efficacy/safety of GH replacement, a pilot study

Guillem Cuatrecasas, Hatice Kumru, Maria Jose Coves & Joan Vidal

Endocrine Connections, 2018, **7**(10): 1031–1039 (DOI: https://doi.org/10.1530/EC-18-0296)

DOI: 10.1530/endoabs.65.JA4

Society for Endocrinology Journal Award – *Clinical Endocrinology*

JA5

Absorption and tolerability of taste-masked hydrocortisone granules in neonates, infants and children under 6 years of age with adrenal insufficiency

Uta Neumann, Martin J Whitaker, Susanna Wiegand, Heiko Krude, John Porter, Madhu Davies, Dena Digweed, Bernard Voet, Richard J Ross & Oliver Blankenstein

Clinical Endocrinology, 2018, **88**(1): 21–29 (DOI: https://doi.org/10.1111/cen.13447)

DOI: 10.1530/endoabs.65.JA5

Early Careers and Plenary Orals

Early Career Prize Lecture Basic Science

EC1.1

Unravelling of new type 2 diabetes genes with 3D chromatin topology analysis and CRISPR-Cas9 perturbations

Ines Cebola[1], Irene Miguel-Escalada[2], Silvia Bonas-Guarch[2], Joan Ponsa-Cobas[1], Goutham Atla[2], Biola Javierre[3,4], Philippe Ravassard[5], Peter Fraser[3,6] & Jorge Ferrer[1,2]
[1]Imperial College London, London, UK; [2]CRG, Barcelona, Spain; [3]The Babraham Institute, Cambridge, UK; [4]Josep Carreras Leukaemia Research Institute, Barcelona, Spain; [5]Université Sorbonne, Paris, France; [6]Florida State University, Tallahassee, USA

Genome-wide association studies have identified nearly 250 loci carrying genetic variants associated with type 2 diabetes (T2D) susceptibility, which are often located within pancreatic islet transcriptional enhancers. Due to the complex nature of transcriptional enhancers, assigning risk variants to true disease susceptibility effector genes has remained a challenge. In this study, we applied promoter capture Hi-C to create a genome-wide map of promoter-enhancer interactions in adult human pancreatic islets. We then set out to investigate which genes are regulated by enhancers carrying T2D risk variants, observing that T2D variants often interact with more than one gene, and that, unlike what has been assumed until now, the nearest genes are not always the true targets of T2D susceptibility variants. We validated our *in silico* predictions by applying CRISPR-Cas9-based methods to perturb T2D enhancers in the human pancreatic ß cell line EndoC-ßH3, demonstrating that the detected enhancer-promoter interactions reflect functional chromatin interactions in human islets. This study reveals 3D chromatin architecture analysis coupled with genome editing as a powerful framework for interpretation of T2D genetic association signals. Furthermore, the results shed light into unexpected regulatory links that may affected by T2D susceptibility variants, bringing to our attention new players in T2D aetiology.

DOI: 10.1530/endoabs.65.EC1.1

Early Career Prize Lecture Translational

EC1.2

From bench to bedside and beyond: a novel therapy to improve wound healing in type 2 diabetes

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The International Diabetes Federation estimates that type 2 diabetes mellitus (T2DM) will affect 642 million people by 2040. Chronically inflamed, hypoxic wounds are common in T2DM and represent a global unmet clinical need. Each year, diabetic foot ulcers cost the NHS £650 million and cause 1 in 200 UK deaths. This mortality is greater than colon, breast and prostate cancer combined. Glucocorticoids are used to treat a range of inflammatory conditions (e.g. asthma, eczema, polymyalgia rheumatica) although long-term therapy is precluded by their adverse side-effects including delayed wound repair and increased infection risk. Glucocorticoid excess drives impaired wound healing through the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) which activates cortisol from cortisone in peripheral tissues including skin. In human skin fibroblasts, we found that 11β-HSD1 regulates over 600 genes in response to inflammation (e.g. suppression of angiogenesis which is essential for effective healing). In these cells, hypoxia (a hallmark of diabetic ulcers) induces 11β-HSD1, which prevents expression of pro-angiogenic vascular endothelial growth factor. In mice, we demonstrated that 11β-HSD1 activity increases during the inflammatory phase of wound healing and topical 11β-HSD1 inhibition improves wound healing during systemic glucocorticoid excess, in aged mice and models of diabetes (importantly, without exacerbation of normal inflammatory responses). Here, I present GC-SHEALD – the first randomized, double-blind, placebo-controlled trial to explore 11β-HSD1 inhibition as a novel therapy for wound healing in type 2 diabetes (https://doi.org/10.1186/ISRCTN74621291).

DOI: 10.1530/endoabs.65.EC1.2

Clinical Endocrinology Trust Best Abstract Clinical

EC1.3

Urine steroid metabolome analysis allows for metabolic risk stratification in 1309 prospectively recruited patients with benign adrenal tumours and different degrees of cortisol excess

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Background
Benign adrenal tumours (AT) can be non-functioning (NFAT) or associated with cortisol excess, as indicated by failure to suppress serum morning cortisol to <50 nmol/l in the 1mg-dexamethasone suppression test (1 mg-DST). The latter group divides into patients with clinically overt signs of cortisol excess (adrenal Cushing's syndrome, CUSH) and patients lacking CUSH signs (mild autonomous cortisol excess, MACE). Smaller series and a recent meta-analysis reported a high prevalence of obesity, type 2 diabetes and hypertension in MACE. However, large-scale prospective data investigating the metabolic impact of MACE are lacking.
Methods
We included 1309 prospectively recruited patients with benign ATs who underwent 1 mg-DST assessment as part of the ENSAT EURINE-ACT study. All patients provided a 24-h urine for mass spectrometry-based urine steroid excretion profiling. Results were compared to 127 healthy controls, using a sex-, BMI- and age-adjusted linear regression model.
Results
NFAT, MACE and CUSH were diagnosed in 50%, 45% and 5% of patients, respectively. Prevalence of metabolic disease increased with the degree of cortisol excess (hypertension: NFAT 64%, MACE 76%, CUSH 72%; type 2 diabetes: NFAT 20%, MACE 28%, CUSH 26%; osteoporosis: NFAT 33%, MACE 47%, CUSH 63%; all $P<0.01$ by Fisher's exact test). Urine steroid metabolome analysis identified specific signatures that correlated with the degree of cortisol excess and clinical outcomes. Patients with cortisol excess, hypertension and diabetes had higher urinary glucocorticoid excretion than those without comorbidities. Patients with cortisol excess and osteoporosis had decreased urinary androgens, suggesting a more pronounced glucocorticoid-induced adrenal suppression.
Conclusions
Cortisol excess is highly prevalent in benign ATs and associated with an increased burden of metabolic comorbidities. The urinary adrenal steroid metabolome provides a tool for metabolic risk stratification and may identify those patients who can benefit from definitive treatment of cortisol excess, e.g. tumour removal in patients with MACE.

DOI: 10.1530/endoabs.65.EC1.3

Clinical Endocrinology Trust Best Abstract Basic

EC1.4

Mice harbouring a germline heterozygous AP2S1 mutation, Arg15Leu, are a model for familial hypocalciuric hypercalcaemia type 3 (FHH3)

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Familial hypocalciuric hypercalcaemia (FHH) comprises three genetic variants: FHH types 1 and 2 are due to mutations of the calcium-sensing receptor (CaSR) and G-protein subunit alpha-11, whereas, FHH type 3 (FHH3) is caused by heterozygous mutations affecting the Arg15 residue (Arg15Cys, Arg15His, Arg15Leu) of the adaptor-related protein complex 2-sigma subunit (AP2S1), which regulates CaSR endocytosis. FHH is usually associated with mild hypercalcaemia, normal parathyroid hormone (PTH) and low urinary calcium excretion. However, FHH3 patients harbouring the Arg15Leu *AP2S1* mutation may have marked and symptomatic hypercalcaemia. To further evaluate the impact of the Arg15Leu *AP2S1* mutation on calcium homeostasis, we used CRISPR/Cas9-mediated gene editing to generate mice harbouring this mutation ($Ap2s1^{+/L15}$). Plasma and 24-h urine was collected for biochemical analysis, and bone mineral density (BMD) was measured by DEXA. These mice were also treated with cinacalcet to assess whether this CaSR positive allosteric modulator can rectify any alterations in calcium homeostasis. All studies were conducted in age-matched adult mice and in accordance with institutional welfare guidelines. Male and female $Ap2s1^{+/L15}$ mice were viable and had marked hypercalcaemia (plasma adjusted-calcium $=2.92\pm0.01$ mmol/l) compared to wild-type mice (plasma adjusted-calcium $=2.33\pm0.01$ mmol/l, $P<0.0001$). This finding was associated with significant hypophosphataemia, hypermagnesaemia, increased plasma PTH, and significantly reduced 24-h urine calcium excretion. Furthermore, male $Ap2s1^{+/L15}$ mice had significantly reduced BMD. Cinacalcet was administered as a 60 mg/kg oral bolus to male and female $Ap2s1^{+/L15}$ mice, and plasma adjusted-calcium and PTH measured at 0, 1, 2 and 4 h post-dose. Cinacalcet suppressed plasma PTH at 1-h post-dose and maximally lowered plasma-adjusted calcium to 2.51 ± 0.02 mmol/l ($P<0.001$ compared to the pre-treatment value of 2.93 ± 0.03 mmol/l) at 2-h post-dose. Thus, these studies have established a mouse model for FHH3, and demonstrate that cinacalcet can be used to treat the marked hypercalcaemia and hyperparathyroidism caused by the Arg15Leu *AP2S1* mutation.

DOI: 10.1530/endoabs.65.EC1.4

Symposia

Gut Hormones Physiology, Pathology and Pharmacology

S1.1

Abstract unavailable.

S1.2

Abstract unavailable.

S1.3

Abstract unavailable.

New Insights into PCOS

S2.1

Fetal antecedents of PCOS: is there a role of AMH?

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Polycystic ovary syndrome (PCOS) is the most common endocrine disorder, affecting 10–18% of women of reproductive age. Based on the Rotterdam consensus, PCOS is diagnosed by at least two of the following three criteria: oligo- or anovulation, hyperandrogenism, and polycystic ovaries on ultrasound. PCOS is also a metabolic disorder since many affected women present with obesity, insulin resistance and associated metabolic comorbidities. Despite its prevalence, the pathophysiology of PCOS is still not understood. Increased androgens levels are considered a key driver in the etiology of PCOS, supported by the development of PCOS-like reproductive and metabolic derangements in various animal models. Women with PCOS also present with 2- to 3-fold increased levels of anti-Müllerian hormone (AMH). AMH is secreted by the granulosa cells of small growing follicles. Since AMH levels correlate strongly with the number of growing follicles, AMH levels are suggested as a marker for PCOS to be used as a proxy for the PCO morphology. Additionally, AMH has been implicated in the pathophysiology of PCOS. AMH suppresses FSH sensitivity of growing follicles, in part by decreasing FSH-induced aromatase expression. It is has therefore been suggested that the increased AMH levels contribute to the anovulatory and hyperandrogenic phenotype of PCOS. However, treatment of mice with AMH did result in a PCOS-like phenotype. Intriguingly, prenatal exposure to excess AMH did induce a PCOS-like phenotype in female offspring. This recent study showed that AMH treatment resulted in an altered intra-uterine environment since AMH exposure decreased placental aromatase expression. As a result, the female offspring were exposed to the elevated maternal testosterone levels during gestation, which in turn induces the PCOS-like phenotype. These studies shed new light on the role of AMH in the pathophysiology of PCOS and warrants further studies on the mechanism of action of AMH.

DOI: 10.1530/endoabs.65.S2.1

S2.2

Abstract unavailable.

S2.3

Abstract unavailable.

Phosphate Homeostasis Physiology, Pathology and Pharmacology

S3.1

FGF23 signalling and physiology

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Fibroblast growth factor 23 (FGF23) is a phosphotropic hormone that belongs along with FGF19 and 21 to a subfamily of endocrine FGFs with evolutionary conserved functions, which can be demonstrated in the gut of C. elegans and in the kidney tubules of fruit flies. FGF23 is posttranslationally regulated by phosphorylation through FAM20C, which causes its proteolysis through the subtilisin-like proprotein convertase FURIN, and results in secretion of FGF23 fragments. O-glycosylation of FGF23 through GALNT3 in turn appears to prevent proteolysis resulting in secretion of the biologically active intact FGF23, that may undergo further processing by plasminogen activators in the circulation. Crystal structures show that the ectodomain of the cognate FGF23 receptor FGFR1c binds with the ectodomain of the co-receptor alpha KLOTHO to create a high affinity binding site for the C-terminal tail of FGF23. The topology of FGF23 furthermore deviates from that of paracrine FGFs, resulting in poor affinity for heparan sulfate, which may explain why FGF23 can diffuse freely in the bone matrix to enter into the bloodstream following it's secretion by cells of the osteoblastic lineage. Intact FGF23 signalling by this canonical pathway activates FRS2/RAS/RAF/MEK/ERK1/2 and reduces serum phosphate by inhibiting 1,25-dihydroxyvitamin D synthesis, which suppresses intestinal phosphate absorption, and by down regulating the transporters NPT2a and NPT2c, which suppresses phosphate reabsorption in the proximal tubules of the kidneys. The physiological role of FGF23 fragments, which may be inhibitory, is currently unclear. Pharmacological and genetic activation of canonical FGF23 signaling causes hypophosphatemic disorders, while it's inhibition results in hyperphosphatemic disorders. In addition, non-canonical FGF23 signaling through binding and activation of FGFR4/calcineurin/NFAT in an alpha KLOTHO independent fashion was reported, which mainly occurs at extremely elevated circulating FGF23 levels, and may contribute to mortality due to cardiovascular disease and left ventricular hypertrophy in chronic kidney disease.

DOI: 10.1530/endoabs.65.S3.1

S3.2

Phosphate-sensing update: interplay between FGF23, phosphate, and phosphate-sensors

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Despite significant progress in understanding the regulation of phosphate (Pi) homeostasis over the past 20 years, the mechanisms underlying the very early step leading to the regulating cascade involving multiple hormones (PTH, vitamin D, FGF23) and organs (kidney, intestine, bone, parathyroid glands) are not deciphered. Progress in this area is based on on the ability to identify and characterise the Pi-sensing mechanism in mammals that allow cells or organisms to detect changes in extracellular Pi levels and trigger appropriate responses. While the molecular players involved in Pi-sensing mechanisms in prokaryotes, yeasts, and plants are well characterised, the molecular actors involved in the detection of Pi in mammals and the mechanisms underlying the Pi-dependent synthesis and/or secretion of FGF23 are poorly defined. We are just beginning to accumulate *in* vitro and *in vivo* data that provide invaluable molecular tools to explore and understand the integrated response of the body to variations in extracellular Pi concentration. Particularly, several molecular actors have recently been involved as potential key players in Pi sensing and Pi-dependent control of FGF23 secretion. Among them, the involvement of PiT1/Slc20a1 and PiT2/Slc20a2 proteins is these mechanisms is standing out. We propose here an updated overview describing the main recent key molecular actors in Pi-sensing and Pi-dependent FGF23 secretion.

DOI: 10.1530/endoabs.65.S3.2

S3.3

FGF23-related hypophosphatemic diseases: prospect for new treatment

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FGF23 is a phosphotropic hormone produced by bone. FGF23 23 reduces serum phosphate by suppressing proximal tubular phosphate reabsorption and intestinal phosphate absorption. Since the identification of FGF23 in 2000, several hypophosphatemic diseases such as X-linked hypophosphatemic rickets (XLH) and tumor-induced osteomalacia (TIO) have been shown to be caused by excessive actions of FGF23. TIO is a paraneoplastic disease and can be cured by complete removal of responsible tumors. However, it is not always possible to find and remove the responsible tumors. XLH is the most frequent cause of genetic hypophosphatemic rickets. Patients with XLH and inoperable TIO have been treated with neutral phosphate and active vitamin D. However, these medications can cause several adverse events such as secondary hyperparathyroidism and gastrointestinal symptoms. The inhibition of FGF23 activity by anti-FGF23 antibodies improved hypophosphatemia, renal phosphate wasting, growth retardation, rickets and reduced grip power of *Hyp* mouse, a model of XLH. Based on these preclinical studies, human monoclonal anti-FGF23 antibody, burosumab, has been developed as a new drug for FGF23-related hypophosphatemic diseases. Several clinical trials indicated that burosumab ameliorates biochemical abnormalities, radiographic findings of rickets and growth in child patients with XLH. Burosumab was also shown to improve hypophosphatemia, fracture healing and histological findings of osteomalacia in adult patients with XLH. Phase 3 studies indicated that burosumab is more effective than conventional therapy. From these results, burosumab has been approved for patients with XLH in several countries. The effects of burosumab in patients with TIO are currently investigated in clinical trials. No serious safety problems have been reported for burosumab. However, it is possible that burosumab use will be restricted because of its high cost.

DOI: 10.1530/endoabs.65.S3.3

Thyroid Hormone a Key Regulator in Inflammation

S4.1

Abstract unavailable.

S4.2

Thyroid hormone in inflammation

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Thyroid hormone levels are strongly affected by inflammation. In a wide spectrum of diseases, ranging from critical illness in the ICU to ischemic stroke, a decrease in circulating T3 and T4 is observed without the expected increase in TSH. This disruption of the negative feedback system of the hypothalamic–pituitary–thyroid (HPT) axis is accompanied by various changes in thyroid hormone metabolism at the cellular and tissue level. Collectively, these changes in thyroid hormone metabolism are known as the non thyroidal illness syndrome (NTIS). The changes in HPT axis feedback are due to increased local bioavailability of T3 in the hypothalamus. This is due to changes in the activity of deiodinase enzymes, which can activate or inactivate thyroid hormone, resulting in increased local T3 concentrations. Besides these changes in circulating thyroid hormones and the HPT axis, NTIS also results in profound changes in cellular thyroid hormone metabolism. These changes are cell type and timing specific and are independent of changes in circulating thyroid hormone, meaning that tissue thyroid levels can differ significantly from serum concentrations. Innate immune cells are important thyroid hormone target cells that play a crucial role during inflammation and infection. In neutrophils, the thyroid hormone inactivating type 3 deiodinase is essential for adequate function both *in vivo* and *in vitro*. In macrophages, the thyroid hormone activating type 2 deiodinase plays an important role. A lack of D2, resulting in lower intracellular T3 concentrations, impairs pro-inflammatory macrophage function. A lack of the thyroid hormone receptor alpha, which modulates the effects of T3, also results in impaired macrophage function and shifts the cells towards a more anti-inflammatory phenotype. Inflammation and infection have profound effects on both central and peripheral thyroid hormone metabolism. Adequate regulation of intracellular thyroid hormone concentrations is crucial for optimal function of neutrophils and macrophages during inflammation.

DOI: 10.1530/endoabs.65.S4.2

S4.3

Myelin repair stimulated by CNS-selective thyroid hormone action

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Thyroid hormone plays a critical role in the production and maintenance of myelin, the lipid-rich sheath that surrounds the outer surface of axons. Myelin is made from processes that extend from oligodendrocytes (OL), a glia cell that comprises about 20% of the cells in the adult central nervous system (CNS). Mature, myelinating OL are produced from a differentiation pathway that begins with neural stem cells and involves the differentiation of oligodendrocyte progenitor cells (OPC), and this final step in the process is regulated by thyroid hormone. Demyelinating lesions in the CNS of multiple sclerosis (MS) patients often contain large numbers of OPC that are unable to differentiate into OL because of an unknown disease associated inhibition of the process. Because there are currently no therapies that stimulate myelin repair for demyelinating diseases like MS, we are pursuing a line of research that asks whether an appropriate thyroid hormone analog can stimulate myelin repair in a mouse model of demyelination. For the thyroid hormone analog, we used the TRß-selective and cardiac and bone sparing thyromimetic sobetirome to avoid the well-known adverse effects associated with chronic hyperthyroidism. We also employed a new prodrug version of sobetirome that increases the blood-brain barrier (BBB) penetration of sobetirome, substantially increasing the amount of drug in the brain while reducing the amount of drug in plasma from a systemic dose. For the demyelinating model we used a novel genetic mouse model (iCKO-*Myrf*) based on inducible and conditional ablation of myelin regulatory factor (*Myrf*), a gene critical for mature OL survival. Induction of *Myrf* knock-out results in essentially complete and CNS-wide disappearance of myelin with a concomitant motor defect phenotype. Results will be presented showing that thyromimetic treatment improves neurological clinical signs and repairs damaged myelin in iCKO-*Myrf* mice.

DOI: 10.1530/endoabs.65.S4.3

Stress - The Rhythm of Life

S5.1

The interplay between stress, biological clocks and metabolic function

Henrik Oster
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In modern societies, the risk of developing metabolic disorders such as obesity or type-2 diabetes is associated with the prevalence of psychosocial stress. Therefore, an improved understanding of adaptive stress responses and their underlying molecular mechanisms is of high clinical interest. In response to an acute stressor, animals activate the sympathetic nervous system and the hypothalamus–pituitary–adrenal (HPA) axis releasing catecholamines and glucocorticoids (GCs) into the circulation. Recent data suggest that stress responses are also regulated by the endogenous circadian clock adapting physiology and behavior to the environmental changes brought about by the Earth's rotation around its axis. Thus, the timing of stress may critically affect adaptive responses to and the pathological effects of repetitive stressor exposure. We have studied the role of different tissue clocks on the regulation of HPA axis activity in mice. We further characterized the impact of predictable social defeat stress during daytime versus nighttime on metabolic regulation and HPA axis activity. Repeated nighttime stressor exposure led to alterations in food metabolization and reduced HPA axis activity with lower circulating adrenocorticotropic hormone (ACTH) and GC concentrations at the time of predicted stressor exposure. Together, our data suggest a circadian gating of stress adaptation at the level of the HPA axis with impact on metabolic homeostasis.

DOI: 10.1530/endoabs.65.S5.1

S5.2

Dynamic of the adrenal in health and disease

Francesca Spiga
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Ultradian rhythms of glucocorticoid hormones is crucial for optimal glucocorticoid-target gene expression, and therefore it is important to understand the mechanisms regulating glucocorticoid pulsatility and how it becomes disrupted in disease. I will discuss our recent findings on how the adrenal steroidogenic pathway responds dynamically to pulses of ACTH, both *in vitro* in adrenocortical cells and *in vivo* in the rat, and how these dynamics become disrupted in response to inflammatory stress resulting in abnormal circulating glucocorticoids levels. I will also show some recent data on the long-term effect of chronic synthetic glucocorticoid treatment on HPA axis dynamics and on adrenal functions.

DOI: 10.1530/endoabs.65.S5.2

S5.3

Abstract unavailable.

New Horizons in Neuro-Endocrine Disease

S6.1

Abstract unavailable.

S6.2

Abstract unavailable.

S6.3

Abstract unavailable.

Early Career Symposia

Engaging with the public

ECS1.1

Abstract unavailable

ECS1.2

Abstract unavailable

ECS1.3

Abstract unavailable

ECS1.4

Abstract unavailable

ECS1.5

Abstract unavailable

What is New?

What is New?

WIN1

What is new in basic endocrinology research?

Caroline Gorvin
University of Birmingham, Birmingham, UK

It is an exciting time to be a basic scientist in endocrinology, with new technologies emerging, increasing opportunities to take advantage of large-scale genetic data, and innovative strategies to translate mechanistic insights into drug discovery and clinical practice. I will discuss what, in my opinion, are the most exciting basic research findings in endocrinology for this year.

WIN2

Abstract unavailable

Clinical Management Workshops

The Clinical Management Workshops are sponsored by
Clinical Endocrinology

Salt & Water

CMW1.1

Management of hyponatraemia

Stephen Ball
Mancheester University Foundation Trust, Manchester, UK

Hyponatraemia is common, present in some 15–20% of non-selected acute hospital admissions in the UK. Hyponatraemia is associated with increased mortality and morbidity across a range of medical problems; emphasising its importance. Despite these factors, the management of patients with hyponatraemia remains challenging. Early recognition of life threatening hyponatraemia (where action is required quickly) is critical. This situation is rare and requires an emphasis on rapid treatment with hyperosmolar fluids rather than detailed investigation. In less critical clinical situations, a systematic approach to differential diagnosis and a stepped approach to course-specific treatment is key. Measurement of both urine osmolality and sodium concentration is pivotal in the differential diagnosis. Common confounders in using these data are concurrent or recent treatment with diuretics, ACE inhibitors or Angiotensin Receptor blockers. This presentation will focus on an evidence-based management strategy for hyponatraemia. It will also highlight common human factors that are obstacles to optimal delivery of care and both strategic and operational approaches to address these over time, improving outcomes and patient experience.

DOI: 10.1530/endoabs.65.CMW1.1

CMW1.2

Diabetes insipidus – management challenges and pitfalls

Mark Hannon
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Diabetes insipidus (DI) is a clinical syndrome characterised by inappropriate hypotonic polyuria. Urine flow rates in excess of 40 mL/kg per 24 h in adults, or more than 100 mL/kg per 24 h in infants are suggestive of diabetes insipidus. Correct diagnosis often requires the use of the water deprivation test. DI may be central or nephrogenic, and results in inappropriate renal water loss. The majority of patients with DI are able to maintain a normal plasma sodium even in the absence of treatment, as their intact thirst mechanism allows them to maintain a sufficient fluid intake to compensate for excessive urinary losses. However, if their thirst sensation is impaired, for example through the presence of a comorbid condition such as a head injury, hypernatraemia will rapidly develop. In the rare condition of adipsic DI, the patient has both a vasopressin secretory defect and an impaired thirst mechanism, commonly resulting in hypernatraemia. Hypernatraemia has multiple adverse physiological effects, predominantly due to the movement of water from cells to the extracellular space, leading to cell shrinkage. If central DI is present then ddAVP (synthetic, long acting vasopressin) treatment needs to be immediately instigated, as well as correction of the patient's volume depletion. Acute central diabetes insipidus is frequently seen in neurosurgical patients. The majority of cases are transient and so a single parenteral (subcutaneous or intramuscular) dose of ddAVP, which is active for six to twelve hours, may be sufficient to provoke antidiuresis and eliminate polyuria. Management of adipsic DI is challenging and requires patients to comply with a strict fluid intake regime. Nephrogenic DI is often medication related and responds to withdrawal of the offending agent. In this session we will examine management challenges relating to diabetes insipidus and potential pitfalls for the clinician to avoid.

DOI: 10.1530/endoabs.65.CMW1.2

CMW1.3

Copeptin – a new player in the diagnosis of salt and water balance

Mirjam Christ-Crain
University Hospital Basel, Basel, Switzerland

Copeptin is secreted in equimolar amount to Arginine Vasopresin (AVP) but can easily be measured with a sandwich immunoassay. Both peptides, copeptin and AVP, show a high correlation. Accordingly, copeptin mirrors the amount of AVP in the circulation and its measurement provides an attractive marker in the diagnosis and differential diagnosis of vasopressin-dependent disorders of fluid homeostasis. This talk will first give some background about copeptin in general and then highlight the use of copeptin for the diagnosis and differential diagnosis of vasopressin-dependent fluid disorders, i.e. Diabetes insipidus on one hand and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) on the other hand.

DOI: 10.1530/endoabs.65.CMW1.3

Hyperparathyroidism

CMW2.1

Management of primary hyperparathyroidism in pregnancy

Rebecca Reynolds
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Primary hyperparathyroidism in pregnancy is rare, with a reported incidence of 1%. It is often asymptomatic with the majority of cases in case-series identified incidentally. Published case series report dramatic maternal complications including nephrolithiasis, pancreatitis, hyperemesis gravidarum, pre-eclampsia and hypercalcaemic crises with fetal complications including intrauterine growth restriction, preterm delivery and neonatal hypocalcaemic tetany. Severity of complications appears proportional to the calcium concentrations though data are limited. In milder cases, plasma calcium levels may be monitored regularly and managed conservatively with adequate fluid intake. In case of very high and increasing calcium levels, and in symptomatic cases, surgical intervention may be indicated. This should be performed in the second trimester if possible. Investigations, differential diagnosis and management will be discussed with illustration from recent cases managed in our antenatal clinics.

DOI: 10.1530/endoabs.65.CMW2.1

CMW2.2

Genetic testing in hyperparathyroidism – who to test and why

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Primary hyperparathyroidism (PHPT) is a common endocrine disorder with a prevalence of 0.86% in Europe. Approximately 10% of cases are hereditary. Syndromic PHPT occurs as part of multiple endocrine neoplasia (MEN)1, MEN4, MEN2A and hyperparathyroidism jaw tumour syndrome. Non-syndromic causes include familial hypocalciuric hypercalcaemia. Establishing the underlying genetic cause allows for targeted, cost effective management. Current guidelines recommend that genetic testing is considered in PHPT with i) age $<$40y, ii) multi-glandular/ recurrent disease, iii) with a personal or family history (FH) suggestive of an endocrine neoplasia syndrome or iv) a FH of PHPT. We reviewed 100 PHPT patients seen in the Cambridge Endocrine Genetics clinic over a 4y period who were referred for multi-glandular disease, relevant FH, Ca:Creatinine clearance ratio (CaCrR) $<$0.01, age $<$50y, or $>$1 risk factor. We offered NGS panel gene testing, including genes *MEN1, CDC73, CASR, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, RET, GCM2, GNA11*, and *AP2S1*. Of the 100 patients, (26 male, 74 female), the mean age was 41.6y (s.d. 17.1). A pathogenic germline variant was identified in 18% (11 *CASR*, 5 *MEN1*, 1 *CDC73*, 1 *AP2S1)* and a variant of uncertain significance (VUS) was identified in 3 patients (all in *RET*). The mean CaCrR was 0.008 in those with a pathogenic variant in *CASR* vs 0.016 in mutation negative group (P 0.003). A CaCrR $<$0.01 had a sensitivity of 95% but poor specificity of 52%. In isolation, age at diagnosis, multi-glandular disease and gender were not predictive of a pathogenic variant whereas a positive FH was a strong predictor of hereditary PHPT. The diagnostic rate was 10.5% in those $>$50 y compared to 18% in those

<50y. In summary, genetic testing is recommended in PHPT *at any* age with i) syndromic PHPT, ii) FH of PHPT or related endocrinopathy, iii) a CaCrR <0.01 and iv) multiple risk factors.

DOI: 10.1530/endoabs.65.CMW2.2

CMW2.3

Challenges in recurrent hyperparathyroidism

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Success following initial parathyroid surgery is high at approximately 95%. Developments in preoperative imaging techniques and subtle variations in parathyroid surgical approach have marginally improved already high success rates. However, failed initial neck exploration or true later recurrence of primary hyperparathyroidism (PHPT) can be difficult to manage. The initial consideration is always to ensure that the diagnosis of PHPT is secure and it is prudent to re-evaluate the biochemical diagnosis before further imaging or attempts at surgery. The recent NICE guideline on primary hyperparathyroidism, NG132, recommends that failed initial parathyroid surgery or recurrences should be managed within an MDT setting of experienced clinicians in parathyroid disorders at centres with such experience and expertise. Imaging modalities may be different in the setting of failed initial neck exploration and certainly the surgical skills required for successfully re-exploring a previously explored neck are different to *de novo* cases. Failure to localise parathyroid adenomas poses significant problems in management and occasionally primary medical therapy such as cinacalcet may be required, at least as a holding measure while further imaging modalities are explored. The threshold for surgical intervention may be different following failed initial neck exploration or later recurrence of PHPT, dependent upon specific circumstances and underlying diagnoses, such as syndromic associations. The talk will cover the difficulties and challenges in managing patients with failed initial neck exploration and later recurrence of PHPT and where feasible, will be based around NICE Guideline 132.

DOI: 10.1530/endoabs.65.CMW2.3

Basic Physiology Workshops

Modelling endocrinology *in vitro*, *in vivo* & *in silico*

BPW1.1

Abstract unavailable

BPW1.2

***In vitro* models of endocrinology: organoids from pituitary and endometrium**

Hugo Vankelecom
KU Leuven (University of Leuven), Leuven, Belgium

The pituitary gland harbors stem cells whose role and regulation remain poorly understood. We recently established organoids from (mouse) pituitary as a novel research model to study pituitary stem cell biology (Cox *et al*., *J Endocrinol* 2019). Organoids represent 3D *in vitro* cell structures that self-develop from tissue stem cells under defined culture conditions, and that reproduce multiple aspects of the original healthy or diseased tissue. Organoids are long-term expandable while retaining their characteristics. The pituitary organoids originate from the $SOX2^+$ stem cells, retain this stemness phenotype during expansive culture and show specific (still limited) hormonal differentiation capacity. This novel organoid model is now used to decipher pituitary stem cell biology at key time points of life as well as after pituitary perturbation (such as transgenic damage which provokes a regenerative response). The endometrium undergoes hormone-regulated cycles of growth, differentiation, degeneration and regeneration. Little is known on the mechanisms that govern these biological remodeling processes, which go awry in endometrial pathology. We established organoid models from healthy human (and mouse) endometrium which were found to display physiological hormone responsiveness, thereby reproducing the menstrual cycle in a dish (Boretto *et al*., *Development* 2017). In addition, we derived organoids from a broad spectrum of endometrial pathologies ranging from hyperplasia to high-grade cancer (Boretto *et al*., *Nature Cell Biology* 2019). The organoids capture the heterogeneity of the disease, both *in vitro* and *in vivo*, and recapitulate genomic abnormalities of the patient's primary tumor. They exhibit disease-specific gene expression signatures and show patient-dependent drug responses. Hence, the new organoid biobank can serve as drug-screening platform to identify better and novel therapies, even in a patient-tailored manner (personalized medicine). In conclusion, we created novel organoid research models for pituitary and endometrium which will be highly valuable to gain more insight into the tissue's biology and pathology.

DOI: 10.1530/endoabs.65.BPW1.2

BPW1.3

Abstract unavailable

Imaging endocrinology from networks to organelles

BPW2.1

***In vivo* imaging of endocrine cell networks**

Patrice Mollard
IGF, CNRS, INSERM, University of Montpellier, Montpellier, France

A major challenge in physiology and pathology is an understanding of the link between the function of a cell population within its tissue environment and its interactions with other organs. The pituitary gland, regulating a diverse range of essential physiological functions, exemplifies this challenge: stimulation from the brain is relayed as variable hormone pulses (the hypothalamic–pituitary (HP) system), which are decoded by peripheral organs into differential effects. The stimulatory inputs and intermediary/final secretory output of the HP system have impressive differences in time-scale and the number of cells involved: a few thousand hypothalamic neurons with signalling frequencies in the millisecond range drive hundreds of thousands of pituitary cells to secrete hormone pulses over a period of hours. These features of the HP system are conserved across a diverse range of mammals. However, how distinct populations of pituitary endocrine cells which are organized in 3D as intermingled cell networks transform hypothalamic inputs into hormone pulses *in vivo* was unknown. The inaccessibility of the pituitary gland, hypothalamus and target organs has led us to develop and adapt a range of methodologies to allow imaging and manipulation of their function with different experimental time-scales and level of control. Using newly-developed techniques for imaging and manipulating cells *in vivo*, namely in freely-behaving mouse models, we unveiled how the pituitary somatotroph network translates its hypothalamic inputs into GH pulses in the bloodstream.

DOI: 10.1530/endoabs.65.BPW2.1

BPW2.2

Spatial programming of GPCR signalling

Aylin Hanyaloglu
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The spatial organisation of receptors at the macro and micro-scale is critical for the tight regulation of cell signalling, including signalling activated by the superfamily of G protein-coupled receptors (GPCRs). To study these processes, a range of imaging techniques have been employed including an increasing application of super-resolution microscopy to image receptor activity beyond the diffraction limit of light. In this session, I will highlight the experimental and imaging approaches we have used to study GPCR signalling at the macro-level, through the identification of divergent endosomal organisation and signalling from a novel endosomal compartment we have termed very early endosomes (VEEs). Furthermore, our studies at the 'micro-level' of GPCR signalling, via the application of super-resolution/single-molecule imaging, has revealed how the organisation of GPCRs in functionally asymmetric oligomeric complexes, impacts both signal sensitivity and diversity. These imaging tools have contributed to our evolved understanding of GPCR signalling, providing models to understand how cells can achieve highly specific diverse downstream responses in dynamic extracellular environments, offer new interpretations of faulty GPCR activity in disease and provide novel therapeutic strategies to target GPCR signalling.

DOI: 10.1530/endoabs.65.BPW2.2

BPW2.3

High content imaging for monitoring signalling dynamics in single cells

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Signalling through intracellular pathways is typically monitored by recording the change in abundance of a signalling component of interest in a whole cell population – often using western blotting. However, single cells differ markedly in their response to a given stimuli, even in a clonal cell line. High content imaging enables signalling responses to be quantified in space and time – in single cells – by the semi-automated imaging of many tens of hundreds of single cells under a multitude of different conditions. The variability in response is likely to be due to each cell having a distinct complement of signalling molecules. Furthermore, this inherent cell–cell variability can be exploited to assess the

contribution of a particular cell component to a signalling pathway using *in silico* cell sorting, without the need for disruptive over-expression or knock-down protocols that push protein expression above or below physiological levels. This *in silico* sorting method will be discussed with respect to expression of the Angiotensin receptor-associated protein (ATRAP) in a human immortalised kidney podocyte cell line. Podocytes are the major constituent cell of the glomerular filtration barrier, but in kidney disease these cells are often injured and lost, resulting in proteinuria. Like other cells in the body, podocytes are prone to receiving damaging signals. ATRAP has been shown to downregulate Angiotensin II signalling, the hormone that regulates blood pressure and is targeted in the treatment of Chronic Kidney Disease to relieve pressure on the kidney tubules. However, further reports indicate that ATRAP interacts with the receptor for TNFα (TNFR1), an inflammatory cytokine. Using immunofluorescence staining followed by *in silico* cell sorting, I will demonstrate that ATRAP disrupts TNFα survival signalling through c-Jun N-terminal kinase (JNK), Nuclear Factor κ-light-chain-enhancer of activated B cells (NF-κB) and its inhibitor, IκBα, in kidney podocytes.

DOI: 10.1530/endoabs.65.BPW2.3

How Do I...?

How do I…? 1

HDI1.1

Abstract unavailable

HDI1.2

Abstract unavailable

HDI1.3

How do I decide which patients with gynaecomastia need more detailed evaluation

Sarah Ali
Royal Free Hospital, London, UK

Gynaecomastia is the proliferation of the male breast glandular tissue and should be distinguished from lipomastia (weight-related fat deposition, also known as pseudogynaecomastia). The development of subareolar ductular tissue and fibrosis in gynaecomastia produces a firmer consistency compared to adipose tissue, which can be differentiated on examination. Gynaecomastia is common and can affect up to two-thirds of adult men. Typically, gynaecomastia arises from an imbalance between the oestrogenic and androgenic effects on the male breast tissue; i.e. due to deficient androgen levels (absolute or relative) or excess oestrogen levels. Whilst it is usually a benign condition, exclusion of serious conditions is important. Benign causes include secondary to certain medications, chronic kidney or liver disease. In addition, hypogonadism (primary or secondary to pituitary disease) or hyperthyroidism, are important common endocrine aetiological causes. Having excluded these causes of gynaecomastia, it is imperative to be vigilant for underlying malignancy causing gynaecomastia. These include oestrogen secreting testicular tumours, oestrogen secreting feminising adrenal tumours and human chorionic gonadotrophin secreting testicular and extra testicular tumours. A careful history and physical examination with simple biochemical testing is adequate for most patients. However, patients with elevated serum oestradiol or human chronionic gonadotrophin (hCG) concentrations require radiological investigations to exclude testicular, adrenal and other extra testicular tumours.

DOI: 10.1530/endoabs.65.HDI1.3

HDI1.4

How do I manage hair loss and hair growth in PCOS

Aled Rees
Cardiff University, Cardiff, UK

Hirsutism and hair loss are common and distressing problems for patients with PCOS. Both are associated with significant psychological impact, including symptoms of depression and reduced quality of life. Treatment options for hirsutism include non-pharmacological approaches (lifestyle change, cosmetic treatments, direct hair removal methods) and pharmacotherapy. Lifestyle change resulting in weight loss can result in modest improvements in Ferriman-Gallwey scores in addition to benefiting other components of the syndrome. Laser therapy and photoepilation are well-tolerated and effective, especially when repeated treatments are given, but benefits have not yet been documented in the long-term. Topical eflornithine, an inhibitor of ornithine decarboxylase, may be effective but only generally in mild cases and treatment may be discontinued if no improvements are seen after 2–4 months of use. Pharmacological treatments include combined oral contraceptives (OCs), anti-androgens and insulin sensitisers, all of which were shown to be superior to placebo in a recent systematic review of randomised controlled trials. Insulin sensitiser monotherapy is less effective than anti-androgens, used alone or in combination with OCs. Evidence suggests that spironolactone, finasteride and flutamide are equally effective as anti-androgen monotherapy, whereas OCs containing cyproterone acetate or drosperinone are no more effective than OCs without anti-androgenic progestins. Topical minoxidil may be considered as an addition to anti-androgen therapy in the presence of androgenic alopecia. Treatment choice needs to be individualised, recognising that prolonged therapy (at least 12 months) is needed for optimal results. The potential for teratogenicity (feminisation of a male foetus) should also be considered when treating a young woman with an anti-androgen, hence strict contraception is mandatory during treatment and for a month after discontinuation.

DOI: 10.1530/endoabs.65.HDI1.4

HDI1.5

Abstract unavailable

HDI1.6

Abstract unavailable

How do I…? 2

HDI2.1

Abstract unavailable

HDI2.2

Abstract unavailable

HDI2.3

Abstract unavailable

HDI2.4

How do I decide when to initiate dopamine agonist withdrawal?

Niki Karavitaki

Institute of Metabolism and Systems Research, University of Bimingham, Birmingham, UK

Dopamine agonists (DA) are the first line treatment for patients with symptomatic prolactinoma and aims to lower prolactin, reduce adenoma size and restore gonadal function. This treatment is effective in the majority of patients and DA resistance s reported in around 10% of patients on cabergoline and 20–30% of those on bromocriptine. Established consensus on the optimal duration of DA therapy is lacking. Given the potential adverse effects of DAs in the long-term and the possibility of remission of hyperprolactinaemia after treatment cessation, a trial of DA withdrawal is included in the management algorithm of prolactinomas. The timing of this has not been clearly established. Current guidelines suggest that treatment may be tapered and subsequently withdrawn in patients who have normal prolactin and no evidence of tumour on imaging and have received DA treatment for at least two years. Nevertheless, the probability of maintenance of remission is low with a meta-analysis showing persisting normoprolactinaemia after DA withdrawal in 21% of micro- and 16% of macroprolactinomas. The recurrences are most likely to occur within a year after stopping DA therapy. Discontinuation of DA therapy can also be considered in females who have reached menopause. The risk of recurrence of hyperprolactinaemia is lower in this group compared with premenopausal women who had a trial of DA withdrawal. Nonetheless, adenoma regrowth has been demonstrated in patients of this group necessitating regular monitoring of the cases with persistent or progressively increasing prolactin values.

DOI: 10.1530/endoabs.65.HDI2.4

HDI2.5

Abstract unavailable

HDI2.6

Abstract unavailable

Innovation Sessions

Advances in Understanding skeletal disease

IN1.1

Identifying new skeletal disease

Outi Mäkitie
University of Helsinki, Helsinki, Finland

Metabolic bone diseases encompass a large spectrum of disorders of bone strength, bone growth, or bone structure. Most of the disorders are caused by genetic defects and have onset prenatally or in childhood. The International classification of genetic skeletal disorders includes >450 disorders divided into 40 subgroups based on their clinical, radiographic and genetic features. The individual disorders are rare but collectively result in significant morbidity and pose a challenge to health care system. Underlying pathology remains inadequately understood in most of these disorders and optimal therapy is often undefined. In order to gain further understanding of the molecular mechanisms leading to the clinical phenotype, research is needed to identify genetic defects and cellular pathology in rare bone diseases. In monogenic forms of osteoporosis, bone fragility is caused by a single mutation in a gene that has a major role in the skeleton. Our research group has identified two novel genetic forms of osteoporosis, caused by *WNT1*and *SGMS2* mutations. WNT1 is a key ligand for the WNT-signaling pathway in the regulation of bone mass and homozygous or heterozygous WNT1 mutations lead to childhood-onset and progressive skeletal fragility. SGMS2 mutations lead to disturbed sphingolipid metabolism, skeletal fragility and defective bone mineralization. The WNT signaling pathway has already proved to be an important drug target whereas the role of sphingolipid metabolism in bone homeostasis remains to be further elucidated. Ongoing genetic studies in several other families with early-onset osteoporosis suggest the presence of multiple other monogenic forms of osteoporosis in which one gene defect plays a major role and other gene variants and life-style factors only play a minor role. Discovery of new genes and unveiling the pathogenetic mechanisms underlying metabolic bone diseases enable development of targeted diagnostic, preventive and therapeutic methods and expands our knowledge on skeletal physiology and pathology.

DOI: 10.1530/endoabs.65.IN1.1

IN1.2

Hyponatraemia and osteoporosis

Joseph Verbalis, Juliana Barsony & Qin Xu
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Numerous epidemiologic studies have associated hyponatremia with both osteoporosis and bone fractures. Disordered bone metabolism with hyponatremia occurs primarily by direct sodium-sensing mechanisms on osteoclasts that are independent from osmolality. Additional effects may be mediated by arginine vasopressin (AVP) receptors on osteoclasts and osteoblasts. Further, even mild hyponatremia can contribute to neurological dysfunction via gait instability and increased falls, both of which compound fracture risk. Accumulating evidence therefore supports the hypothesis that sodium homeostasis is an important component of bone metabolism. Although the cellular mechanisms are yet to be fully identified, studies in rats and cultured cell demonstrated that reducing the sodium concentration ($[Na^+]$) causes osteoporosis primarily by increasing osteoclast formation from precursors by activation of the RANK/PI3K/Akt/m-TOR pathway. More recent studies have identified immediate index responses to low $[Na^+]$ (120 mmol/l) in mature osteoclasts from primary murine bone marrow macrophages and murine RAW264.7 pre-osteoclastic cells, including: 1. Increased cellular GTP-bound Rac1 GTPase, detected through specific protein interaction with the Pak1 protein-binding domain. Specificity of the GTP-bound Rac1 response was confirmed by similar assays on GTP-bound Rho with the Rhotekin binding domain and GTP Ras with the Raf1 protein binding domain. 2. Increased cellular lysosome acidity, detected by increased fluorescence emission after 5, 15, and 30 min, peaking at 45 min in response to low $[Na^+]$, whereas no change was detected in normal $[Na^+]$ samples. Correcting the low $[Na^+]$-induced membrane hyperpolarization by adding equimolar choline chloride (20 mmol/l) did not prevent the increase in lysosomal acidification. These data indicate that mature osteoclasts rapidly respond to low $[Na^+]$ with GTPase activation, likely from a G-protein-mediated low $[Na^+]$-sensing mechanism with subsequent triggering of acid production promoting resorption of bone matrix. Controlled clinical trials are needed to address whether reversing disorders of sodium homeostasis can improve individual patient and population-based skeletal health.

DOI: 10.1530/endoabs.65.IN1.2

IN1.3

Abstract unavailable.

Big Data in Space and Time

IN2.1

Single cell technologies in endocrine systems

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Single cell (sc) technologies offer an unprecedented level of investigation into cellular heterogeneity. Transcriptomic analyses are most commonly performed, but genome and epigenome can also be investigated at the sc level. Moreover, multi-omics technologies are developed to profile simultaneously different material from the same cell, enabling for example correlations between genomic mutations and alteration of gene expression. In parallel, spatial transcriptomics aim to combine transcriptomic and morphological information. The large amount of data generated require sophisticated bioinformatic analyses to extract biological meaning. Different algorithms are used to reconstitute cellular hierarchies along a pseudo-time axis offering a chance to characterise new, previously invisible, intermediate cell states.Genome and transcriptome sc technologies are commercially available, therefore these analyses are accessible to researchers. The focus will be placed here on transcriptome analyses, exploring the unique possibilities they bring, but also remaining hurdles. The requirements and pipeline for sample preparation will be discussed, along expected outcomes and modalities of analysis and resolution. Significant advances provided by sc analyses will be discussed, in the field of cancer, stem cell research and endocrine organs. In tumour, cellular hierarchies can be reconstructed from sc genomes, allowing resolution to the cell(s) and mutation(s) at the origin of the disease. This maybe the only way to identify rare cell types, such as cancer stem cells and circulating tumour cells, and therefore better characterize mechanisms of resistance to treatments, and of tumour reoccurrence. In stem cell research, characterisation of differentiation pathways is a central question to improve disease modelling and drug screening assays, and ultimately for regenerative medicine. Pseudo-time analyses have already provided invaluable information, for example in pancreatic islets, to improve protocols for b-cells differentiation. Most endocrine organs have now been examined using sc RNAseq, revealing novel information about known cell types, and also new cellular subpopulations.

DOI: 10.1530/endoabs.65.IN2.1

IN2.2

Abstract unavailable.

IN2.3

Abstract unavailable.

NIHR Pathways to Clinical Impact

IN3.1

From basic science to life changing therapies

Waljit Dhillo
Imperial College London, London, UK

Endocrinology is fascinating as new hormones are being discovered every year with the power of genomics and scientific advances. The physiology of these novel hormones needs to be investigated in animal studies to determine their mechanism of action and efficacy. These essential animal studies can then highlight potential translational potential of novel hormones. The next step in this translational pathway is first into human studies followed by studies in patient cohorts to demonstrate the efficacy of novel hormones as potential new therapeutics. This translational pathway has been limited due to funding for early phase human studies of novel hormones. However since the formation of the National Institute for Health Research (NIHR) working closely with the Medical Research Council (MRC) since 2006 UK researchers have benefitted from the potential funding available to be able to carry out studies in animals of a novel hormone and then investigate the effects of these hormones in first into human studies. Importantly, funding is now also available to take these novel hormones and test them in patient cohorts for efficacy and then work with pharma to make new drugs to benefit our patients with endocrine pathologies. Over the last decade basic science discovery led to the discovery of the kisspeptin/neurokinin/dynorphin expressing neurones (KnDy neurones) in the brain as major regulators of the reproductive axis. Funded by the MRC and NIHR for the last 15 years I will describe the route from basic science discovery, first into human studies and then onto studies in patient groups to which have led to kisspeptin based therapes for the potential treatment of infertility as well as neurokinin antagonists as potential new treatments for menopausal flushing.

DOI: 10.1530/endoabs.65.IN3.1

IN3.2

Abstract unavailable.

IN3.3

Abstract unavailable.

Meet the Expert Sessions

Thyroid disease after immune reconstitution
MTE1

Abstract unavailable

Functional imaging of the adrenal
MTE2

Abstract unavailable

Updates on DSD genetics
MTE3

Update on DSD genetics

John Achermann
UCL GOS Institute of Child Health, London, UK

Since the discovery of *SRY* as the main testis-determining gene more than 25 years ago, at least 30 other single gene conditions have been identified that can result in differences/disorders in sex development (DSD). Some of these are associated with 'classic' steroidogenic blocks or related conditions such as CAH, whereas others are associated with alterations in gonad determination and development. Reaching a specific genetic diagnosis can have implications for understanding the condition, the need for monitoring associated features, defining tumour risk and fertility options, as well as counselling an individual and their family about inheritance patterns. A genetic approach may be the only way to reach a specific diagnosis, especially when there are no pathognomonic biochemical tests available, or in the adult clinic when gonadectomy may have been performed or when information about historic investigations may be limited. In this session, I will review the mechanisms and pathways underlying sex development in humans; provide an overview of the classification of DSD; highlight some recent advances in the field (e.g. NR5A1/SF-1, DHX37) and discuss the relative contribution of different causes in the paediatric and adult clinic. We will consider some circumstances where genetic diagnosis is important, and also how new technologies such as next generation sequencing and single-cell RNASeq can help us to understand mechanisms and reach a genetic diagnosis more quickly.

DOI: 10.1530/endoabs.65.MTE3

Fighting liver fat
MTE4.1

Fighting liver fat

Jeremy Cobbold[1] & Jeremy Tomlinson[2]
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Non-alcoholic fatty liver disease (NAFLD) is the most highly prevalent chronic liver condition and is associated with significant adverse outcomes, both through liver-specific morbidity and mortality, but perhaps more importantly, through adverse cardiovascular and metabolic outcomes. NAFLD is a spectrum of disease, extending from simple steatosis, through to inflammation and fibrosis and risk of cirrhosis. The mechanisms that govern hepatic lipid accumulation and the predisposition to inflammation and fibrosis represent a complex interplay between metabolic target tissues including adipose and skeletal muscle, and immune and inflammatory cells. NAFLD is tightly associated with type 2 diabetes and obesity, both driving progressive disease towards the most advanced stages. It is also associated with other endocrine conditions including hypogonadism in men and polycystic ovary syndrome in women. Accurate diagnosis and staging are crucial as they provide prognostic information that impacts upon clinical management. Liver biopsy is still regarded as the gold-standard investigative tool; however, there are now an array of novel non-invasive biomarkers and imaging modalities that aim to accurately reflect the stage of underlying disease and their use will be discussed. Licensed therapies for NAFLD are currently lacking, although data are emerging from phase 3 clinical studies indicating that specific liver-targeted therapies are close to becoming available. Our current strategy is to advocate an holistic, multidisciplinary approach to patient management, combining aggressive lifestyle intervention to promote weight loss with cardiovascular risk reduction, focussing on blood pressure control, hyperlipidaemia, smoking cessation and optimization of blood glucose control (preferentially using agents with a positive impact on weight, liver, cardiovascular risk as well as glycaemic control).

DOI: 10.1530/endoabs.65.MTE4.1

MTE4.2

Abstact unavailable

Novel epigenetic inhibitors
MTE5

Abstract unavailable

What have we learned from HR-pQCT?
MTE6

What have we learned from high resolution peripheral quantitative computed tomography (HR-pQCT)?

Jennifer Walsh
University of Sheffield, Sheffield, UK

HR-pQCT assesses peripheral sites (distal radius and distal tibia). The technique has all the advantages of quantitative CT; it makes a volumetric assessment of bone mineral density (rather than the areal measurement made by DXA), it is less affected by overlying soft tissue than DXA, and it can separate cortical and trabecular compartments. Because it measures peripheral sites in a purpose-built device, it can use high energy radiation to obtain high resolution images, with a low effective radiation dose. The voxel size was about 80 microns in the first generation scanners and 60 microns in the second generation. This resolution can image trabecular and cortical microstructure, to quantify trabecular number, thickness and structural homogeneity, and cortical porosity. Before HR-pQCT this level of microstructural detail could only be obtained *in vivo* by bone biopsy. HR-pQCT images can also be reconstructed into Finite Element models, for virtual testing of bone stiffness and strength. The earliest clinical studies gave new insights into age- and gender-specific changes in bone microstructure. For example, in men, trabecular thickness decreases with ageing but trabecular number is preserved, whereas in women, trabecular number decreases which has a greater impact on bone strength. HR-pQCT studies have increased our understanding of bone fragility in young women with idiopathic osteoporosis and obese children, as well as in older adults. They have also helped to understand the mechanism of action of different osteoporosis drugs. HR-pQCT is unlikely to become a widely-used clinical technique, but it is an important addition to the research tool kit.

Recommended reading:

Clinical imaging of bone microarchitecture with HR-pQCT. Nishiyama KK, Shane E. *Curr Osteoporos Rep* 2013 11:147–55. doi: 10.1007/s11914-013-0142-7

Osteoporosis drug effects on cortical and trabecular bone microstructure: a review of HR-pQCT analyses. Lespessailles E, Hambli R, Ferrari S. *Bonekey Rep*. 2016;5:836. doi: 10.1038/bonekey.2016.59.

DOI: 10.1530/endoabs.65.MTE6

Clinical Skills

Being a consultant - How to get the job and keep it

SK1.1

How to get the consultant post you want

Christine May
Oxford University Hospital, Oxford, UK

I hope to be able to offer some advice and guidance having only recently attained my consultant post last year. The decision of where you are going to start your consultant career is potentially the largest decision you have made regarding your career to date. So, how can you prepare yourself to stand the best chance against other competitors in the field? By breaking the process down I will cover the following areas-

– The benefits of trying to optimise your CV in the run up to your consultant post. There are various extra areas you could work in the last 12–18 months of your registrar post that would make you stand out from the other people applying.
– Finding a consultant post.
– Choosing your consultant post, you may know exactly what you want from your post, you may be limited by geographical location or specialist interest, or you may be less clear, I will show how I worked through this decision.
– Finally the interview itself. You may not have been to interview for the last 5 years, if not longer, so what can you do to prepare for it, and what is the structure?

DOI: 10.1530/endoabs.65.SK1.1

SK1.2

Abstract unavailable

SK1.3

How do I set up a new service?

Andrew Lansdown
University Hospital of Wales, Cardiff, UK

Setting up a new service begins with identifying patient *needs* at both a local and national level, with the goal of producing higher quality and more sustainable services, improved health outcomes, reduced health inequalities and better models of care. *Aims and objectives* of the new service need to be clearly laid out early on, with the support and input from all stakeholders to ensure its wider acceptance and long-term success. *Building* a business case is vital in explaining why the new service Is needed and should be clinically-led, underpinned by clear clinical evidence base and national standards. The scale of service, financial implications, organisations involved and geographical focus should be carefully described. Commissioners, patients, public and staff should be engaged throughout the process to ensure full support of the clinical community. *Implementation* of the new service must take into account service access, scope of referrals, staffing, training needs, location, facilities, health informatics, use of current resources, sustainability, publicity, patient safety and clinical governance issues. Key areas of continuing professional development, training, education and ongoing service expansion need regular and frequent review. *Evaluation and improvement* of the new service are both vital, measuring its ongoing effectiveness and evolving the service in line with current guidelines and best practice. Communication of the new service to others, its successes and challenges, should be disseminated at both a local and national level, to enable improved quality of patient services offered across the wider healthcare system and encourage others to use similar models in their own scope of practice.

DOI: 10.1530/endoabs.65.SK1.3

Basic Skills

Introduction to teaching

SK2.1

Abstract unavailable

SK2.2

Abstract unavailable

Teaching Skills

Innovations in teaching

SK3.1

Innovations in teaching

Sohag Saleh & James Moss
Imperial College, London, UK

In higher education, endocrinology teaching is often delivered by academic researchers and endocrine physicians, however their involvement in teaching is rarely the primary focus of their job plan. As such, opportunities to develop as an educator are often triaged behind primary responsibilities such as research, funding applications, publications and patient care. Undergraduate and postgraduate medical education is delivered across a range of settings (classroom, lab, bedside), with tutors responsible from teaching groups as small as one or as large as several hundred. Learning opportunities must focus on established local and national syllabi, and adequately prepare students for associated assessments (i.e. you can read 100 books on driving but passing your driving test would be challenging without hours of experience behind the wheel). Typically, traditional approaches to teaching at UK universities have been didactic, linear and tutor-centred. However, recent changes in funding, governance and policy are driving improvements in the design and delivery of teaching, which is becoming increasingly dynamic, collaborative and interactive. There are many evidence-based strategies that enable tutors to design and deliver effective interactive sessions, and careful planning, resource preparation and choreography enable educators to deliver constructive sessions that facilitate learning. This workshop will explore a flexible low-tech approach to education that is scalable across a range of teaching settings. We hope that attendees can draw on this to develop their own teaching skills.

DOI: 10.1530/endoabs.65.SK3.1

SK3.2

Abstract unavailable

Nurse Sessions

NICE & T3

NS1.1

T3 replacement – What does the evidence suggest?

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Hypothyroidism is one of the commonest endocrine disorders, affecting about 3% of the adult population. Levothyroxine (T4) is the standard treatment for hypothyroidism and is one of the most commonly prescribed drugs in the UK. Whilst most patients with hypothyroidism are satisfied with this treatment, a small subgroup of patients do not feel well on T4 monotherapy. Whether such patients would benefit from Liothyronine (T3), taken either in combination with T4, as a monotherapy or as a component of desiccated animal thyroid extract, remains controversial. This controversy has further escalated in recent years due to a huge increase in the price of T3 in the UK, and wide variations in the clinical practice and policies of clinical commissioning groups across the country in relation to the prescription of T3. Several randomised control trials and subsequent meta-analyses have failed to show a clear-cut benefit of T3–T4 combination therapy over T4 monotherapy. However, limitations of these clinical trials include small sample sizes, relatively short follow-up periods, and use of variable and non-physiological dosage of T3. The recently published draft NICE guidelines on thyroid diseases recommend not to routinely offer T3 for primary hypothyroidism, either alone or in combination with T3, because of not enough evidence that it offers benefits over T4 monotherapy. This presentation will discuss evidence for and against the use of T3 in subgroup of patients with hypothyroidism.

DOI: 10.1530/endoabs.65.NS1.1

NS1.2

Health care professional & patient consultation – informed decision making

Antonia Brooke
Royal Devon and Exeter Hospital, Exeter, UK

Shared, informed decision making is a key component to high quality care in the NHS. This can occasionally be challenging through lack of time, lack of high-quality trial evidence to support treatment choices and financial limitations to treatment. Informed decision making includes open discussion of the risks and potential adverser consequences of treatment and alternatives. People with endocrine disorders often have symptoms that encompass both their psychological and physical health, and as part of collaborative care it is important that these are explored during the consultation. Research suggests that patients with chronic endocrine conditions report not being listened to and this is a barrier to effective consultation. We know that patients come into healthcare consultations with their own expectations and agenda, which may or not match with the healthcare professional's provisional agenda. A dissonance between the patient and the HCP can be a significant barrier in informed decision making. An essential aspect of the consultation is for patients to be able to disclose their concerns, and seek information and support. If this need isn't met it is likely the consultation will be less helpful and may not meet the patients physical and psychological needs. This talk will explore the basis of informed decision making as well as reviewing some ideas relevant to complex consultation such as supporting patients who have unresolved symptoms.

DOI: 10.1530/endoabs.65.NS1.2

NS1.3

A Beginners Guide: setting up a Nurse-Led Thyroid Clinic

Jean Munday
Queen Alexandra Hospital, Portsmouth, UK

This talk is aimed at nurses who wish to set up nurse-led clinics. Although the focus will be on thyroid clinics the principles could be used for other conditions. Consideration will be given to the practicalities of establishing a new clinic, the process and the clinical expertise required. The Society for Endocrinology Competency Framework for Adult Endocrine Nursing underpins the knowledge and skills required by Endocrine Nurses running their own clinics. https://www.endocrinology.org/careers/training-and-resources/guides/society-for-endocrinology-competency-framework-for-adult-endocrine-nursing-2nd-edition/

DOI: 10.1530/endoabs.65.NS1.3

Management of Hyper and Hypocalcaemia

NS2.1

Abstract unavailable.

NS2.2

Patient management of hypercalcaemia and when should the surgeon intervene?

Neil Gittoes
Centre for Endocrinology, Diabetes and Metabolism, Birmingham, UK

Hypercalcaemia is common and can represent a broad spectrum of underlying diseases that range from common to extremely rare. Furthermore, causes of hypercalcaemia can be mild and indolent or may be rapidly progressive and represent serious underlying diseases such as cancers. It is thus important to have a clear understanding of hypercalcaemia, particularly its early assessment and management that will lead to a diagnosis of the underlying cause. Hypercalcaemia can present as an emergency or may be a consistent finding on laboratory tests over a protracted period. The talk will cover acute management of hypercalcaemia, diagnostic work up and a focus on differential diagnoses. Longer term management of endocrine causes of hypercalcaemia will be explored, particularly primary hyperparathyroidism. The recent NICE guideline on primary hyperparathyroidism (PHPT), NG132, will be reviewed with an emphasis on investigations to exclude mimics of PHPT, considerations around the role of surgery and a rational approach to imaging prior to surgery. Use of bisphosphonates and cinacalcet will also be explored in patients with PHPT. A plan for longer term follow up of patients with PHPT will be proposed, encompassing those who have and those who have not received successful parathyroid surgery. The utility of genetic testing in patients with PHPT will also be covered.

DOI: 10.1530/endoabs.65.NS2.2

NS2.3

Patient management of hypocalcaemia & the patient perspective

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Acute hypocalcaemia can be a serious and potentially fatal medical emergency while chronic hypocalcaemia may be debilitating and is often associated with reduced quality of life. The usual aetiology of hypocalcaemia is hypoparathyroidism which is sufficiently rare to be officially recognised as an 'orphan' condition. Other causes of hypocalcaemia include vitamin D deficiency and hypomagnesaemia secondary to proton pump inhibitor therapy. The relative rarity of hypoparathyroidism and its status as an orphan condition seem to be associated with frequent sub optimal management of this condition leading to significant morbidity in this patient group. Despite the availability of authoritative and well validated guidelines for managing both acute and chronic hypocalcaemia data continue to show poor outcomes. In this presentation, I will summarise the aetiology and physiology of hypocalcaemia, review current treatment guidelines for management of hypocalcaemia and focus on the patient perspective of living with hypocalcaemia in order to raise awareness of the condition and to emphasise the quality of life impact that it can have and the need for improved treatment. I will also promote the valuable role of the patient support group Parathyroid UK in supporting patients living with this condition.

DOI: 10.1530/endoabs.65.NS2.3

Endocrinology in the UK

Workforce, Standards, and Quality Improvement

ROE1.1

Abstract unavailable

ROE1.2

Getting it right first time for endocrinology

John AH Wass
Oxford University, Oxford, UK

There are 126 departments of adult endocrinology in England. We will be producing a national report towards the end of the year joint with the Society for Endocrinology. Endocrinology is not properly coded in hospital data systems. This is because of misattribution to general medicine or diabetes. Commonly accepted clinical standards are not being applied uniformly (e.g., steroid sick day provision). We have looked at surgical volumes. There are a large number of places where small volumes of adrenal surgery are being carried out. Doing phaeochromocytomas and adrenal cancer the recommended number is approximately 20 and if it is not the above adrenal pathologies 6 or more based on Fausto Palazzo's work. There are 24 neurosurgical units operating on the pituitary. Figures vary. Most departments are operating on more than 30 pituitaries a year but some are dealing with much smaller numbers. There is wide variance in the number and skills of the endocrine specialist nurses. They are underutilised for clinical care, testing and education and can be a cost-effective addition to the team. Appointment of a specialist nurse would be advantageous in many services. Tier 3 obesity services (multidisciplinary obesity care but not bariatric surgery) should be present in all centres according to NHS England. Currently this is the situation in 55% of hospitals in the country. The results from GIRFT endocrinology will provide a baseline of current endocrine practice in England and robust recommendations will be made to address inequalities and inadequacies in service provision. GIRFT has already helped centres reflect on practice and develop business cases to address shortfalls in resource. Furthermore it will provide an impetus for sharing best practice to help provide a higher standard of care for all endocrine patients nationally.

DOI: 10.1530/endoabs.65.ROE1.2

ROE1.3

SfE/ABCD/DUK – diabetes and endocrinology consultant workforce survey: results from 2018

Stella George
East and North Herts Institute of Diabetes and Endocrinology, Stevenage, UK

The diabetes and endocrinology consultant survey has been running for a number of years aiming to look at workforce issues faced by our speciality. It started originally as a paper based survey that was sent out to all consultants in the UK but has since migrated to an online survey hosted by the Royal College of Physicians which is sponsored by three societies – The Society for Endocrinology, The Association of British Clinical Diabetologists and Diabetes UK. The aim of this talk is to reveal the results of the most recent survey held in 2018 – with supportive information from the RCP workforce unit and others. It will highlight the trends that have been developing in the working lives of consultants in diabetes and endocrinology throughout the UK in the past years by discussing issues that affect our day to day work – time spent on call, on the general wards, in specialty clinics, academic work etc. but also reveal such data as the reasons why colleagues choose to retire. As well as data about consultant colleagues, data regarding trainees such as recruitment into the speciality, are also shown.

DOI: 10.1530/endoabs.65.ROE1.3

ROE1.4

Abstract unavailable

ROE1.5

Abstract unavailable

Senior Endocrinologists' Session

SE1.1

What happened to the adrenal X-zone?

Malcolm Peaker

13 Upper Crofts, Ayr, UK

After its first description in 1924, and naming by Evelyn Howard in 1939 to reflect its transient and unknown function, the X-zone of the mouse adrenal attracted a great deal of attention from endocrinologists. What factors were responsible for its appearance at the age of 8–12 days, growth, and then disappearance with puberty in the male and first pregnancy in the female? A great deal was discovered, even given the limited techniques available, about which hormones control, directly or indirectly, the X-zone. Its function, however, remained unknown with the possible production of steroid hormones apparently eliminated. Having worked briefly on the Z-zone in 1965—my only foray into the adrenal—I took the opportunity of retirement to look up what had happened in research on the X-zone. Had the enigma of its function been solved? I was surprised that although seemingly isolated bits of research had added to knowledge of systemic and putative local factors controlling the life and death of the cells, and an enzyme concerned with steroid catabolism had been found in the zone, knowledge of the X-zone has not progressed to any significant extent since the 1980s. We still do not know what it does. Mice are not the only mammals to have seemingly special cells forming unusual zones in their adrenals. I will, therefore, point out the importance of a comparative approach while describing the historical evidence on X-zone control and function, including relations between the adrenal medulla and cortex, while stressing the importance of understanding how whole organs—and whole animals—work. The X-zone remains Zone 'X'.

DOI: 10.1530/endoabs.65.SE1.1

SE1.2

Is the estrogenic component of Premarin all bad?

Richard Santen

University of Virginia, Charlottesville, USA

The Women's Health Initiative studies reported that the menopausal hormone therapy (MHT) regimen containing conjugated equine estrogen (CEE) and medroxyprogesterone acetate increased, whereas CEE alone reduced breast cancer incidence. These observations suggest the possibility that CEE might exert unique actions on breast and also suggest the need to eliminate the progestogen from MHT regimens. A MHT regimen called a tissue selective estrogen complex (TSEC), containing CEE plus bazedoxifene (BZA), to avoid the need for a progestogen, was developed and FDA approved. We testing the effects of this TSEC *in vitro* and *in vivo*, we found unique properties of CEE which could make if a much more favorable estrogen formulation for women starting on menopausal hormone therapy. We asked whether CEE exerts effects on breast cancer which differ from those of estradiol (E_2) A human breast cancer cell line (MCF-7) and wo rodent models (NMU and ACI) were used to compare the effect of CEE with E_2 on mammary tumor formation, proliferation and apoptosis. In both the NMU and ACI models, E_2 significantly increased tumor incidence and multiplicity whereas in striking contrast CEE did not, even though the estrogenic effects of CEE and E_2 on uterine weight were identical. Mechanistically E_2 blocked whereas CEE stimulated apoptosis (cleaved caspase-3) in ACI animals and only E_2 stimulated proliferation (Ki67). BZA exerted highly potent anti-estrogenic effects on tumors by completely blocking palpable tumor formation. These data suggest that the CEE/BZA TSEC may be a safer, breast-antagonistic, MHT agent for women and might have potential to prevent breast cancer while relieving menopausal symptoms.

DOI: 10.1530/endoabs.65.SE1.2

SE1.3

Potential benefits of adequate vitamin D status for non-bony disorders are large, so why do so many RCTs of supplementation fail?

Barbara Boucher

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Cross-sectional and prospective data reveals significant dose-wise health-risk reductions with higher vitamin D status, each with proven mechanistic explanations. RCT causality confirmation is sparse but support is emerging with better appreciation of vitamin D's biology. Confounding factors in vitamin D RCT design include that nutrients are not pharmaceuticals [increases in serum 25(OH)D concentrations and efficacy with supplementation of deficiency are 'S'-shaped, sizeable biological effects being seen along the steep parts of the 'S' but not in repletion or uncorrected deficiency]; self-supplementation; unassessed dietary intake, sun exposure; unknown baseline/achieved Vitamin D status; genetic variation and unchecked compliance. Analyses on initially deficient subjects using 'Individual Participant Data' are revealing significant health benefits within supposedly failed RCTs & RCT meta-analyses [e.g. URTI's fall by 70% and mortality by 25%], suggesting RCTs should supplement deficiency and achieve adequacy. Circulating 25(OH)D concentrations regulate target tissue vitamin D_3 formation [not PTH], explaining their consistent associations with health-benefits. Benefit-thresholds vary observationally and in RCTs [e.g. ~50 nmol/l for bone-health, ~80 nmol/l for lowering insulin resistance]. Assay data varies widely despite compliance with international quality control schemes and HPLC/TMS assays are higher than immunoassays [by +5–33 nmol/l]. Thus, harmonization of immunoassay to HPLC/TMS data raises both thresholds and diagnostic cut-offs, requiring internationally agreed rationalization of these parameters. Low fat foods and ageing reduce vitamin D absorption. Other nutrients modulate calcitriol's efficacy [e.g., excess vitamin A reduces VDR activation; magnesium deficiency impairs vitamin D activating enzymes; calcium inadequacy reduces calcitriol's rapid non-genomic actions] while vitamins D_2 and D_3 differ biologically]. Genetic variations affect 25(OH)D binding to DBP, VDR activity and efficacy of vitamin D activating enzymes – thereby modulating serum 25(OH)D concentrations. Overall, therefore, vitamin D RCTs should aim to allow for these factors to improve their outcome reliability.

DOI: 10.1530/endoabs.65.SE1.3

Oral Communications

Metabolism and Obesity

OC1.1

Intracrine activation of 11-oxygenated androgens by AKR1C3 modulates lipid metabolism in human female adipose tissue

Lina Schiffer[1], Alexandra J Sinclair[1], Michael W O'Reilly[1], Connar Westgate[1], Afeefa Mashood[1], Elliot Palmer[2], Lorna C Gilligan[1], Rishi Singhal[3], Angela E Taylor[1], Warwick B Dunn[4], Wiebke Arlt[1] & Karl-Heinz Storbeck[5]
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Polycystic ovary syndrome (PCOS) affects 10% of women and is associated with an increased risk of type 2 diabetes and fatty liver disease. Androgen excess is an important driver of metabolic risk in PCOS. In adipose tissue from women with PCOS, increased activation of androstenedione (A4) to testosterone (T) by the enzyme AKR1C3 results in systemic lipotoxicity. Recent *in-vitro* studies also demonstrated that T and 11-ketotestosterone (11KT) activate the androgen receptor with similar potency and that AKR1C3 activates 11-ketoandrostenedione (11KA4) to 11KT with higher efficiency than A4 to T. Furthermore, 11-oxygenated androgens including 11KT constitute the majority of circulating androgens in PCOS. Here, we examined intra-adipose activation of classic and 11-oxygenated androgens and their differential metabolic impact. We performed *ex-vivo* primary adipose tissue incubations of paired subcutaneous (sc) and omental (om) samples obtained from eight women undergoing bariatric surgery (age 32–59 years; BMI 44–57 kg/m^2). Incubations with A4 and 11KA4, respectively, revealed significantly higher AKR1C3-mediated conversion of 11KA4 to 11KT than conversion of A4 to T. Untargeted metabolome analysis by mass spectrometry revealed differential adipose tissue metabolic responses, with predominant alterations of glycerophospholipid metabolism in sc adipose, which were more pronounced in response to 11-oxygenated than classic androgens. Co-incubation of adipose explants with 11KA4 and a selective HSD11B1 inhibitor significantly enhanced the activation of 11KA4 to 11KT by decreasing the HSD11B1-catalysed inactivation of 11KA4 to 11β-hydroxyandrostenedione. Urinary steroid profiling by gas chromatography-mass spectrometry in 8 women (age 23–35, BMI 25–49) treated for 12-weeks with a HSD11B1 inhibitor demonstrated the expected reduction in glucocorticoid activation, but also a significant shift in the ratio of urinary 11-oxygenated androgen metabolites towards the active keto-derivatives, reflective of increased activation of 11-oxygenated androgens. We conclude that local activation of 11-oxygenated androgens is the predominant source of androgen exposure in adipose tissue and enhances systemic lipotoxicity.

DOI: 10.1530/endoabs.65.OC1.1

OC1.2

Hepatic *de novo* lipogenesis is suppressed and fat oxidation is increased by omega-3 fatty acids at the expense of glucose metabolism

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Background and Aim
Hepatic *de novo* lipogenesis (DNL) has been implicated in the development of non-alcoholic fatty liver disease (NAFLD). Supplementation with the omega-3 fatty acids (FA) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) decreases intrahepatic triacylglycerol (IHTAG) and plasma TAG concentrations, which is suggested to be mediated through changes in hepatic DNL. We investigated the effects of omega-3 FA supplementation on intrahepatic DNL and FA partitioning using a combination of human *in vivo* and *in vitro* cellular studies.
Methods
Thirty-eight healthy males were randomised to take either an omega-3 supplement (4 g/d EPA + DHA as ethyl esters) or placebo (4 g/d olive oil) for 8 weeks; fasting measurements were made at baseline and 8 weeks. The metabolic effects of omega-3 FAs on IHTAG content, hepatic DNL and FA partitioning were investigated using metabolic substrates labelled with stable-isotope labelled tracers. *In vitro* cellular studies, using a human liver cell-line were undertaken to gain insight into the intrahepatocellular effects of omega-3 FAs.
Results
Body weight remained unchanged in both groups. Fasting plasma TAG concentrations decreased ($P<0.01$) in the omega-3 FA supplementation group and remained unchanged in the placebo group. Eight weeks of omega-3 FA supplementation decreased ($P<0.05$) IHTAG, fasting and postprandial hepatic DNL whilst increasing ($P<0.05$) dietary FA oxidation and plasma glucose concentrations. *In vitro* cellular studies demonstrated both EPA + DHA were required for the intrahepatocellular effect.
Conclusions
Omega-3 FA supplementation had a potent effect on decreasing hepatic DNL with concomitant increases in FA oxidation and plasma glucose concentrations. Attenuation of hepatic DNL may be considered advantageous; however consideration is required as to what the potential excess of non-lipid precursors (e.g. sugars) will have on intra- and extra-hepatic metabolic pathways.

DOI: 10.1530/endoabs.65.OC1.2

OC1.3

Metabolic and functional effects of fatty acid overload on *in vitro* tissue engineered skeletal muscle

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Introduction
Efficient fuel selection between glucose and fatty acids in insulin-sensitive organs is a key feature which determines metabolic health in humans. In skeletal muscle, lipid storage and utilisation can differ between healthy and diseased individuals, however to date there are limited *in vitro* models to explore this. Therefore, aim of this work was to investigate the effects of nutrition on engineered skeletal muscle health and metabolism.
Methods
Three-dimensional tissue engineered skeletal muscles were developed by seeding C2C12 myoblasts into Collagen/Matrigel® solution between 3D printed inserts. Initially cultured for 4 days in growth media followed by 10 days in differentiation media (DM), muscles were then exposed to fatty acid-free BSA alone or conjugated to Oleic, Palmitic, Linoleic, and α-Linoleic Acids (OPLA; physiological ratio 45:30:25:1%) at concentrations of 200 μM or 800 μM for 4 days. Constructs were stained and analysed for lipid droplets and functional capacity was measured by electrical field stimulation. Engineered muscles were also analysed for changes in the mRNA expression of lipid metabolism and storage genes, the expression of mitochondrial and insulin signalling proteins, and morphological changes.
Results
Exposure to OPLA increased the presence of lipid droplets in a dose dependent manner. There was a significant increase in Perilipin 2 and a dose dependent increase Pyruvate dehydrogenase lipoamide kinase isozyme 4 mRNA expression. PGC-1α protein increased with increasing OPLA concentration yet citrate synthase expression remained unchanged. In addition, the increase in the presence of lipid droplets resulted in a reduction force generation and altered the insulin signalling response.
Conclusions
Exposure to OPLA induces lipid droplet accumulation in tissue engineered skeletal muscle as well as increase the expression of key lipid storage and oxidation markers. The presence of lipid droplets also impairs maximal contractile force production in this system.

DOI: 10.1530/endoabs.65.OC1.3

OC1.4

5β-reductase (AKR1D1) is downregulated in patients with non-alcoholic fatty liver disease and protects against hepatocellular carcinoma cell proliferation *in vitro*

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Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of metabolic syndrome. It is a spectrum of disease ranging from simple intracellular

lipid accumulation and eventually progressing to cirrhosis and hepatocellular carcinoma (HCC). 5β-reductase (AKR1D1) is highly expressed in human liver and catalyzes a fundamental step in bile acid (BA) synthesis. BAs are established as potent regulators of metabolic phenotype and we have hypothesised that AKR1D1 plays a crucial regulatory role in NAFLD and HCC. Human liver biopsies were obtained from 34 obese patients. Genetic manipulation of AKR1D1 was performed in human HepG2 and Huh7 hepatocellular carcinoma cell lines. mRNA and protein expression changes were determined using qPCR, RNA-sequencing and western blotting. Effects on cell proliferation and cell cycle were determined using CyQuant, flow cytometry, transcriptome analysis, and enzyme immunoassays. In human liver biopsies, *AKR1D1* expression decreased with advancing steatosis, inflammation and fibrosis and was significantly reduced in patients with type 2 diabetes. In HepG2 cells, RNA sequencing analysis, following transient *AKR1D1* knockdown, identified discrete dysregulated pathways impacting lipid metabolism, DNA replication, cell cycle and p53 signalling. In both cell lines, *AKR1D1* knockdown decreased BA synthesis with a consequent downstream decrease in cyclin-dependent kinase (CDK1, CDK2, CDK4, CDK6) and proliferation markers expression (CDC6, PCNA, PLK1). In contrast, expression of cyclin-dependent kinase inhibitors (CDKIs: p15, p16, p21) increased. Endorsing these data, HepG2 cells with stable knockdown of *AKR1D1* proliferated more slowly with evidence of cell cycle arrest on flow cytometry. Pharmacological manipulation of BA receptor activation prevented the induction of CDKIs gene expression, suggesting that the observed phenotype is driven, at least in part, through BA and/or oxysterol availability. In conclusion, AKR1D1 is down-regulated with advancing NAFLD and inhibits hepatocellular carcinoma cell proliferation *in vitro*. Taken together, these data suggest an as yet unexplored role of AKR1D1 in the progression of NAFLD to HCC.

DOI: 10.1530/endoabs.65.OC1.4

OC1.5

Prolyl-hydroxylase 3 maintains β-cell glucose-sensing under metabolic stress

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Aims
Prolyl-4 hydroxylase domain protein 3 (PHD3) is an alpha ketoglutarate-dependent dioxygenase involved in the oxygen-dependent regulation of cell phenotype. While PHD3 has been reported to suppress insulin sensitivity in the liver, little is known about effects of the enzyme in insulin-secreting β-cells.
Methods
βPHD3$^{-/-}$ mice were generated by crossing the Ins1Cre driver line with animals bearing a floxed *Egln3* gene (encoding PHD3). Ca^{2+} fluxes, ATP/ADP dynamics, insulin secretion and metabolic tracing were assessed using Fluo8, Perceval, HTRF assay and GC–MS, respectively.
Results
PHD3 loss under standard chow did not affect insulin secretion, Ca^{2+} fluxes and ATP/ADP ratios, and this was mirrored by normal glucose homeostasis *in vivo*. After four weeks HFD feeding, however, βPHD3$^{-/-}$ mice were glucose-intolerant, despite improved glucose-stimulated insulin secretion (GSIS) from isolated islets. $^{13}C_6$ mass isotopomer distribution analysis of HFD βPHD3$^{-/-}$ islets showed an increase of glucose incorporation into m+3 lactate, indicating reduced input of glycolysis into the tricarboxylic acid (TCA) cycle. The following observations were suggestive of a switch to utilisation of fatty acids in HFD βPHD3$^{-/-}$ islets: 1) ATP/ADP responses to glucose were halved; 2) glucose-driven ATP/ADP ratios could be rescued by inhibiting the fatty acid transporter CPT1; 3) glucose incorporation into lipid pools was decreased; and 4) chronic incubation with fatty acid to supply acetyl-CoA to the TCA cycle was able to amplify GSIS. By eight weeks HFD, βPHD3$^{-/-}$ islets presented with markedly impaired Ca^{2+} and insulin responses to glucose.
Summary
Specific loss of PHD3 in β-cells leads to dependence on fatty acid metabolism, eventually leading to insulin secretory failure. Thus, PHD3 might be a pivotal component of the β-cell glucose-sensing machinery by disallowing use of fatty acids as a primary fuel source under metabolic stress.

DOI: 10.1530/endoabs.65.OC1.5

OC1.6

Metabolic surgery reduces kidney SGLT2 expression in mice

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Imperial College London, London, UK

Background
Both metabolic surgery and sodium glucose co-transporter (SGLT2) inhibitors have been demonstrated to improve insulin sensitivity and glucose clearance, but also increase glucagon secretion and cardiovascular health.
Aim
To examine the effect of metabolic surgery (Vertical Sleeve Gastrectomy; VSG) on SGLT2 expression in kidney cortex of lean mice.
Methods
In order to assess whether exogenous SGLT2 inhibition has the same euglycemic effects as bariatric surgery, 14 lean mice underwent VSG ($n=8$) or sham ($n=6$) surgery. Glucose (3 g/kg) tolerance tests with or without treatment with the SGLT2 inhibitor dapagliflozin were performed four weeks post operatively. Kidneys were harvested from fed mice and analysed using Quantitative real-time PCR (qRT-PCR) and immunofluorescence.
Results
Quantitative RT PCR and immunofluorescence analysis on mouse kidneys demonstrated a significant lowering of SGLT2 expression at both the protein ($n=5$, $P=0.0007$) and mRNA ($n=7$, $P<0.0001$) levels four weeks after VSG. VSG did not cause any weight loss when compared to sham operated mice ($P=0.37$, Mann-Whitney test). Nevertheless, VSG mice displayed significantly improved glucose tolerance ($P<0.001$) and insulin secretion ($P<0.01$), which was not further affected by dapagliflozin (10 mg/kg; $P>0.05$). In contrast, treatment of sham mice with dapagliflozin increased glucose tolerance, though to a lesser extent than VSG. Glucagon levels were elevated post VSG and post treatment with dapagliflozin in both VSG and sham groups ($P<0.01$). Glycosuria was observed in 2/5 VSG mice, yet not in controls.
Conclusions
Our previous results on the effects of Duodenal Jejunal Bypass in lean rats showed a significant lowering of SGLT2 expression, confirming that both gastric and intestinal surgery in lean animals causes a significant inhibition of SGLT2 in the kidney cortex. These findings point towards a physiologically-relevant gut-kidney axis. SGLT2 inhibition may thus be an important mechanism through which bariatric surgery improves glucose tolerance in man.

DOI: 10.1530/endoabs.65.OC1.6

Neuroendocrinology, Pituitary and Neoplasia

OC2.1

Differential effects of subcutaneous pulsatile versus oral hydrocortisone replacement therapy on fMRI resting state and task based emotional processing in patients with primary adrenal insufficiency

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Background
Patients with primary adrenal insufficiency (PAI) describe significant impairments in quality of life. Current replacement regimes are non-physiological. Animal studies indicate that pulsatile presentation of endogenous glucocorticoids is critical for normal transcriptional and behavioural responses. Healthy volunteer work also shows that pattern of glucocorticoid presentation alters cognitive and emotional processing.
Objective
To assess the effects of glucocorticoid presentation on cognition and emotional processing in patients with PAI
Methods
The Pulses study (ISRCTN67193733) was a 6-week Double-blind placebo control cross over trial of standard three-time daily oral hydrocortisone to continuous pulsatile subcutaneous in PAI secondary to Addison's (AD) and Congenital Adrenal Hyperplasia (CAH) ($N=21$, AD 17/CAH 4). Secondary outcome measures of resting state and task based (Facial Expression Recognition Task – FERT) functional magnetic resonance imaging (fMRI) are discussed. Whole brain and region of interest (ROI) analysis based on known cortisol sensitivity and involvement in emotional processing was performed. Washout range 6 weeks-1 year. Total daily dose of hydrocortisone was the same on both arms (range 20–40 mg).

Results
Righthanded $N=13$ female AD only; fsl analysis detected differential activation between treatment arms. Task based whole brain analysis under fearful condition – Middle Frontal Gyrus, Precentral Gyrus, Superior Frontal Gyrus, Supplementary Motor Cortex, Anterior Cingulate Gyrus and Paracingulate Gyrus. ROI analysis under fearful condition – insula and amygdala. Resting state fMRI ROI analysis dorsal striatum and insula.
Conclusions
The Pulses trial confirms safety and tolerability of subcutaneous hydrocortisone pump treatment. No subjects dropped out due to trial related issues. fMRI detected differentially activated executive control regions that are important in cognitive and emotional processing. This gives an early indicator that cortisol dynamics impact on cognition and emotional processing and should be considered in glucocorticoid based therapeutics.

DOI: 10.1530/endoabs.65.OC2.1

OC2.2

Investigating the role of *AIP* in pituitary tumourigenesis

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Introduction
Germline mutations in the aryl hydrocarbon receptor interacting protein (*AIP*) gene predispose to growth hormone (GH, 90% of patients) or prolactin (PRL)-secreting tumours, with negligible number of patients with other pituitary tumour types. Animal models of acromegaly are scarce and *Aip* models have controversial data. Therefore we have generated two pituitary-specific *Aip* knockout mouse models to study the consequences of loss of AIP protein and understand its role in tumourigenesis.
Models and phenotype
Our $Aip^{Flox/Flox};Hesx1^{Cre/+}$ model abrogates *Aip* in cells expressing the early pituitary transcription factor *Hesx1*, specifically targeting the anterior pituitary cells from E8.5. The inducible $Aip^{Flox/Flox};Sox2^{CreERT2/+}$ model deletes *Aip* upon administration of tamoxifen exclusively in *Sox2*-expressing cells, which form the pituitary stem-cell niche.
Results
The $Aip^{Flox/Flox};Hesx1^{Cre/+}$ model mirrors the human phenotype, showing an increased body size, enlarged organs (e.g. heart), high circulating IGF-1 and 85% penetrance of functional pituitary tumours at 15 months. Contrastingly, the tamoxifen-inducible *Sox2*-based model showed no increased body size or altered IGF-1 up to 18 months from injecting at 3 or 8 weeks old. A developmental abnormality localised in the pituitary intermediate lobe (IL) is observed in at least 50% of $Aip^{Flox/Flox};Hesx1^{Cre/+}$ embryos and tamoxifen-injected $Aip^{Flox/Flox};Sox2^{CreERT2/+}$ adults. Furthermore, tamoxifen-injection during pregnancy resulted in embryonic IL abnormality, recapitulating the $Aip^{Flox/Flox};Hesx1^{Cre/+}$ embryonic phenotype. The observed abnormality consists of ectopic PIT-1, GH and PRL-expressing cells in the IL Moreover, some of the tumours in adult animals arise from these altered cells of the IL.
Conclusions
Our data suggest that *Aip* loss leads to a pituitary development defect with ectopically expressed GH and PRL, ultimately promoting tumourigenesis. This supports the clinical observations, that *AIP* mutation positive patients invariably develop disease during childhood and there is a lack of somatic *AIP* mutations in pituitary tumours. Overall, this highlights AIP's key role in tumours and normal pituitary development.

DOI: 10.1530/endoabs.65.OC2.2

OC2.3

ErbB receptor signalling in MCF7 breast cancer cells: an information theoretic approach

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Epidermal growth factor (EGF) and heregulin (HRG) act via ErbB receptors, to stimulate Akt and ERK. These drive breast cancer cell proliferation and the network is targeted in cancer therapy (1). Single cell responses show marked cell-cell variation and information theory provides statistical measures that take the effect this noise has on information transfer into account (2). Here we quantify the mutual information (MI) between stimulus concentration and effects in MCF7 cells as measures of information transfer, activating ErbB1 homodimers with EGF and ErbB2-ErbB3 heterodimers with HRG, and then using single cells measures of pAkt or ppERK (immunofluorescence staining and high content imaging) to calculate MI values (I(response;stimulus)). EGF caused the expected increases in pAkt and ppERK that were transient (maximal at 5 min and lost by 60 min) whereas HRG caused sustained increases in both. Maximal I(ppERK;-stimulus) and I(pAkt;stimulus) values were comparable (~0.7Bit). Both values mirrored kinetics of the population averaged phosphorylation responses (maximal at 5 min for EGF and comparable at 5–60 min for HRG) indicating that cell-cell heterogeneity does not scale with the population averaged responses, and when both responses were measured in parallel, joint sensing increased MI values by only ~0.1 Bit. Thus, using this novel approach to quantify information transfer via ErbB receptors reveals that individual MCF7 cells are unreliable sensors of EGF and HRG concentration (with most information lost through signalling), and that concomitant activation of these two effectors does not greatly increase information transfer whereas agonist-induced receptor internalisation (that is rapid for ErbB1 homodimers but not for ErbB2-ErbB3 heterodimers) does reduce it in this model.
References
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DOI: 10.1530/endoabs.65.OC2.3

OC2.4

Investigating the role of vagal Y2R in PYY_{3-36}-mediated appetite suppression

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Introduction
The gut hormone peptide YY 3-36 (PYY_{3-36}) is secreted postprandially from intestinal L-cells to signal satiety. Peripheral administration of PYY_{3-36} suppresses food intake in rodents and humans. PYY_{3-36}-based drugs are therefore promising anti-obesity treatments. It has been proposed that circulating PYY_{3-36} supresses appetite via the Y2 receptor (Y2R) in the hypothalamic arcuate nucleus (ARC). The vagus nerve, the major link between the gut and the brain, also expresses Y2R but its role in PYY_{3-36} signalling is poorly understood. We hypothesised that PYY_{3-36} physiologically reduces food intake by activating vagal afferent signalling and does not activate central appetite/nausea-altering pathways to have an effect.
Methods
We generated an afferent vagus nerve-specific Y2R knockdown (KD) mouse model. Adult $Y2R^{loxP/loxP}$ mice were bilaterally injected in the nodose ganglion (NG) of the vagus nerve with an adenoassociated virus (AAV) encoding the Cre recombinase (AAV-Cre). To study the central Y2R, adult $Y2R^{loxP/loxP}$ mice were bilaterally injected with AAV-Cre in the ARC. Heterozygous littermates injected with a GFP-expressing AAV were used as controls.
Results and Conclusions
Quantification of Y2R mRNA in NG, which contains only the cell bodies of vagal afferents, demonstrated >70% KD of Y2R in AAV-Cre-injected $Y2R^{loxP/loxP}$ mice (NG-Y2R-KD) compared with controls. This is, to our knowledge, the first example of selective Y2R vagal deafferentation. Intraperitoneal injection of PYY_{3-36} at low dose decreased food intake in control groups, but this effect was abrogated in NG-Y2R-KD. PYY_{3-36} administration at a high dose resulted in appetite suppression in all experimental groups, including ARC-Y2R-KD. High resolution food intake analysis revealed a significant difference in meal patterning rather than total food intake in the NG-Y2R-KD group. These results suggest that the afferent vagus nerve contributes to mediating the physiological effects of PYY_{3-36} but that alternative signalling pathways might be more important in mediating its pharmacological effects.

DOI: 10.1530/endoabs.65.OC2.4

OC2.5

Efnb2 controls pituitary gland development by regulating proliferation of the pituitary stem/progenitor cells and EMT within the pituitary stem cell niche

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Efnb2 encodes for the ligand Ephrinb2 that binds to its cognate Eph receptor, with which plays an integral role in angiogenesis, stem cell regulation and tumorigenesis. Using a pituitary-specific Cre-driver ($Hesx1^{Cre}$), we conditionally deleted *Efnb2* from the early stem/progenitor cells (PSCs) of the developing pituitary gland. We found that *Efnb2* is expressed in PSCs both during embryogenesis and adulthood, suggesting its involvement in PSCs maintenance. Here we show that genetic ablation of *Efnb2* ($Efnb2^{fl/fl};Hesx1^{Cre/+}$) results in severe pituitary hyperplasia, abnormal gland morphogenesis and delay in the terminal differentiation of hormone-producing cells. In order to understand the underlying molecular mechanisms by which *Efnb2* deletion leads to pituitary abnormalities during embryogenesis, we performed transcriptomic analyses using mRNA-Seq at early stages of pituitary development on $Efnb2^{+/+}$ and $Efnb2^{-/-}$ cell populations. Interestingly, unsupervised gene set enrichment analyses of the transcriptomic results identified *Efnb2* as a key negative regulator of PSCs proliferation, whilst involved in the regulation of epithelial integrity and epithelial to mesenchymal transition (EMT). Functional assays performed to validate transcriptomic analyses revealed that *Efnb2*-null PSCs hyper-proliferate both *in vitro* and *in vivo* and downregulate the expression of genes involved in EMT, indicating a role of *Efnb2* in these two developmental pathways. Indeed, whilst *Efnb2*-null PSCs within the marginal zone hyper-proliferate, they downregulate genes of epithelial integrity, resulting in an abnormal EMT transcriptomic profile. Additionally, these events leads to a significant delay of the pituitary cell lineage commitment program, determining severe reduction in the expression of Pit1, Pomc1 and Gsu commitment markers. Taken together, our results reveal a novel role for *Efnb2* (Ephrinb2) as key regulator of pituitary gland development. *Efnb2* negatively regulate the proliferation of pituitary stem/progenitor cells while controlling the epithelial integrity of the stem cell niche and regulating EMT.

DOI: 10.1530/endoabs.65.OC2.5

OC2.6

Post-operative copeptin analysis as a predictor of diabetes insipidus after pituitary surgery

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Background
Diabetes insipidus (DI) is a recognised complication of pituitary surgery, with current diagnosis requiring clinical observation aided by plasma and urine electrolytes and osmolalities. Copeptin, a 39 amino acid glycopeptide secreted in equimolar quantities to ADH, is a stable surrogate marker of ADH release and has potential to facilitate prompt diagnosis of post-operative DI. This assay has been shown to accurately predict which patients are likely to develop DI following pituitary surgery. We aimed to trial use of copeptin as a predictor of post-operative DI risk in our centre.
Objective
To determine whether copeptin analysis can be used to predict which patients are at risk of developing DI following transsphenoidal adenomectomy (TSA).
Methods
44 patients undergoing TSA had samples taken for copeptin pre-operatively, and subsequently at day 1, day 2, day 8, and week 6 post-TSA. Results from patients who developed post-op DI (based on clinical assessment, urine and plasma biochemistry and the need for treatment with DDAVP) were compared to those who did not. Patients with any evidence of pre-operative DI were excluded.
Results
Of 44 patients assessed, eight were clinically determined to have developed DI. Differences were observed between patients with DI and those without in post-operative samples. Of note, there was a significant difference at day 1 post-operation ($P=0.025$ on Kruskal–Wallis test), with no samples in the DI group exceeding 3.5 pmol/l (100% sensitivity, 52.9% specificity at this cut off).
Conclusion
We confirm that early post-operative copeptin analysis in TSA patients can help to predict the risk of developing diabetes insipidus. In this setting, co-peptin is a useful rule-out test in patients with values above a defined threshold, which may facilitate earlier decision making and shorter hospital stays.

DOI: 10.1530/endoabs.65.OC2.6

Bone and Calcium

OC3.1

A mouse model generated by CRISPR-Cas9 with a frameshift mutation in the nuclear factor 1/X (*NFIX*) gene has phenotypic features reported in Marshall-Smith Syndrome (MSS) patients

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Marshall-Smith syndrome (MSS) is a congenital disorder characterised by developmental delay, short stature, respiratory difficulties, distinctive facial features, skeletal abnormalities (such as kyphoscoliosis, dysostosis and osteopenia) and delayed neural development, and is due to heterozygous mutations that are clustered in exons 6–10 of the transcription factor nuclear factor I/X (*NFIX*) gene. These frameshift and splice-site *NFIX* variants result in the production of aberrant transcripts that escape nonsense mediated mRNA decay and lead to the production of dominant negative mutant NFIX protein. To elucidate the *in vivo* effects of mutant *NFIX*, CRISPR-Cas9 was used to generate a mutant mouse model with a frameshift deletion of 2 nucleotides (*Nfix* Del2) in *Nfix* exon 7. All animal studies were ethically performed under an approved UK Home Office Animal License. $Nfix^{+/Del2}$ mice were viable, normal and fertile but $Nfix^{Del2/Del2}$ mice had significantly reduced viability ($P<0.002$), and died at 2–3 weeks of age. Phenotypic characterisation of the 2–3 weeks $Nfix^{Del2/Del2}$ mice showed that, compared to $Nfix^{+/+}$ and $Nfix^{+/Del2}$ mice, $Nfix^{Del2/Del2}$ mice had significantly reduced: growth rate (0.8-fold, $P<0.05$); tail length (0.9-fold, $P<0.001$); lean (0.8-fold, $P<0.0001$) and fat (0.4-fold, $P<0.0001$) mass; weight (0.8-fold, $P<0.0001$); and total tissue mass (0.8-fold, $P<0.0001$). Moreover, >30% ($P<0.0001$) of $Nfix^{Del2/Del2}$ mice had kyphosis compared to <10% $Nfix^{+/+}$ and $Nfix^{+/Del2}$ mice, and micro-CT scans of the lumbar and thoracic vertebrae revealed $Nfix^{Del2/Del2}$ mice to have osteopenia. In addition, plasma biochemistry analysis of $Nfix^{Del2/Del2}$ mice revealed that, compared to $Nfix^{+/+}$ and $Nfix^{+/Del2}$ mice, $Nfix^{Del2/Del2}$ mice had significantly: increased plasma urea (1.4-fold, $P<0.0001$) and total bilirubin (1.5-fold, $P<0.0001$) concentrations; and alkaline phosphatase activity (1.5-fold, $P<0.0001$); but decreased procollagen type 1 *N*-terminal propeptide (0.8-fold, $P<0.01$) concentrations. Thus, $Nfix^{Del2/Del2}$ mice provide a useful model for studying the skeletal, renal and hepatic effects of mutant *NFIX* and the mechanisms underlying the aetiology of MSS.

DOI: 10.1530/endoabs.65.OC3.1

OC3.2

Hypophosphatasia in adulthood - are patients really 'unaffected'

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Introduction
Hypophosphatasia (HPP) is a very rare systemic musculoskeletal disease characterised by low tissue non-specific alkaline phosphatase (ALP). The prevalence of HPP and its associated morbidity in an adult setting is unclear.
Methods
A search for serum ALP results less than 36 IU/l within NHS Greater Glasgow and Clyde between 2017 and 2018 revealed 16 280 results. A further search for

patients with two ALP <36 separated by 30 days or more yielded 1143 patients over the age of 18 years. Of these, 706 patients with conditions known to be associated with low ALP were excluded (62%) as were another 129 patients who were over 80 years old. The patient characteristics of the remaining cohort were identified using electronic health care records. Rate of symptoms were calculated using the frequency of symptoms over the cumulative lifespan of patients.

Results

A total of 312 patients were identified as having persistently low ALP. 4 had an existing diagnosis of HPP (1.3%). The median age was 50 years (18–80), where 64% were female and 91% of British/Scottish ethnicity. The cohort was divided into ALP quartiles and their key characteristics are summarised in the table below:

			Rate of symptoms (per10 000 person years)					
Lowest ALP (quartiles)	*N*	Known HPP Diagnosis (%)	All Fractures	Dental	Psychia-tric	Joint Pains	Neuro-logical	Hearing loss
all	312	4 (1.3)	37.89	11.00	22.82	33.21	20.98	8.56
5–20	76	4 (5.3)	66.23	24.37	45.30	41.85	10.33	10.33
21–24	75	0	27.15	2.65	16.33	21.84	16.33	8.17
25–27	75	0	45.41	10.60	34.61	10.60	40.01	24.01
28–34	66	0	31.67	12.71	18.96	44.17	18.96	12.71

Conclusions

Our survey has identified a sizeable number of adults who have persistently low ALP. In these cases, fractures and non-specific joint pains were the most common symptoms and similar to that reported in the global HPP registry (Högler *et al*, 2019). There is a need to improve the awareness as well as identification of HPP within the health care setting.

Reference

Högler *et al*. Diagnostic delay is common among patients with hypophosphatasia. *BMC Musculoskelet Disord* 2019;20(1):80.

DOI: 10.1530/endoabs.65.OC3.2

OC3.3

Generation of a long acting parathyroid hormone hybrid analogue through fusion to a binding protein

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Hypoparathyroidism causes severe hypocalcaemia and defective skeletal metabolism. Treatment with calcium and vitamin D supplementation can cause kidney failure whilst native parathyroid hormone (PTH) requires repeated injections and causes renal impairment paralleling high peak and low trough PTH levels. A long-acting PTH, providing constant physiological levels, is needed. LA-PTH, a hybrid of PTH and PTH related peptide, prolongs cAMP responses via altered receptor mechanisms.[1] Protein fusion to growth hormone binding protein (GHBP) delays clearance.[2] Fusing LA-PTH to GHBP could generate an improved long-acting PTH.

Methods

LA-PTH fusions were gene-synthesised and stable CHO clones generated using Invitrogen's Flp-In system. Large-scale roller bottle protein expression was followed by purification using ion-exchange and affinity chromatography. Sample analysis by Coomassie staining & western blotting followed SDS-PAGE. A Dual Luciferase Reporter Assay in rat Osteosarcoma (UMR-106) cells assessed potency. The ligands' ability to generate cAMP at times after ligand washout was assessed via competitive ELISA following cAMP generation assays.

Results

Two fusions were constructed and their sequences confirmed: LA-PTH-1 is LA-PTH linked to GHBP and PTH receptor extracellular domain; LA-PTH-2 is LA-PTH linked to GHBP. Western blotting on stably transfected CHO cell media, using an anti-GHBP antibody, confirmed expression: LA-PTH-1 and LA-PTH-2 separated as diffuse bands between 100-75 kDa and 50-37 kDa respectively. 1.49 mg/mL LA-PTH-1 and 0.42 mg/mL LA-PTH-2 was expressed. LA-PTH-1 (EC50 mean ± SD: 222 ± 133 nM) was ~30-fold less potent than PTH-1-34 (8 ± 3), however, LA-PTH-2 (14 ± 2) was approximately equipotent. Fusion longevity of action profiles resembled PTH-1-34, however LA-PTH-2 accumulated ~3-fold PTH-1-34 cAMP levels (equimolar challenge, 100 nM); area under the curve ~15 000 vs. ~5000 pmol/well.

Conclusion

It is possible to express and purify two PTH hybrid analogues in a mammalian cell line whilst retaining *in-vitro* bioactivity. Longevity of action testing is ongoing; future work will examine in-vivo bioactivity and pharmacokinetics.

DOI: 10.1530/endoabs.65.OC3.3

OC3.4

Characterisation of rare *GNA11* variants reveals 8 novel residues important for signalling by the calcium-sensing receptor: Relevance for FHH and ADH

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The calcium-sensing receptor (CaSR) is a G-protein coupled receptor that predominantly signals via $G\alpha_{q/11}$-mediated pathways to regulate extracellular calcium (Ca^{2+}_e) homeostasis. Germline $G\alpha_{11}$ inactivating and activating mutations cause familial hypocalciuric hypercalcaemia type-2 (FHH2) and autosomal dominant hypocalcaemia type-2 (ADH2), respectively. To date, four FHH2 and six ADH2 mutations have been reported. To identify novel variants, we investigated large-scale sequencing databases (ExAc, dbSNP), comprising 60,706 exomes from unrelated individuals and the DiscovEHR cohort, comprising exomes from 51 289 patients with matched phenotyping data. We identified 91 missense variants and selected 14 ($n=9$ ExAc/dbSNP; $n=5$ DiscovEHR) variants predicted to be pathogenic for functional analysis. Wild-type (WT) or variant *GNA11* expression constructs were transiently expressed in CaSR-expressing HEK293A $G\alpha_{q/11}$ knockout cells, with $G\alpha_{11}$ protein expression confirmed by Western blots. Functional effects on CaSR-mediated intracellular calcium (Ca^{2+}_i) release and MAPK activity were assessed using nuclear factor of activated T-cells response element (NFAT-RE) and serum response element (SRE) luciferase reporter constructs, respectively. Two ExAc/dbSNP variants (Gly51Arg and Arg213Trp) significantly reduced NFAT-RE and SRE activity in response to 8 different increasing concentrations of Ca^{2+}_e (up to 4.2-fold; $P<0.001$), whereas a Gln152His variant significantly increased NFAT-RE and SRE activity (up to 1.6-fold; $P<0.01$), when compared to WT, consistent with these being loss- and gain-of-function variants, respectively. In addition, three variants (Gly66Asp, Arg147Cys and Ala231Thr) significantly increased NFAT-RE reporter activity (up to 2.4-fold; $P<0.001$) but had no significant effect on SRE response. Two (Arg37Leu and Arg210Trp) of the five DiscovEHR cohort variants identified in patients with mild hypercalcemia (mean plasma calcium >10mg/dL) significantly decreased NFAT-RE and SRE activity (up to 6.5-fold; $P<0.001$), thereby indicating they likely represent novel FHH2-causing mutations. Thus, our study, which reveals eight novel, rare $G\alpha_{11}$ variants affecting two different components of CaSR-mediated signalling, indicates that the prevalence of FHH2 is ~4 per 100 000 individuals.

DOI: 10.1530/endoabs.65.OC3.4

OC3.5

Mutational analysis of a patient with familial hypocalciuric hypercalcaemia identifies a novel p.Ser182Cys mutation, which is predicted to disrupt the calcium sensing receptor (CaSR) extracellular domain

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Familial hypocalciuric hypercalcaemia (FHH) is an inherited disorder of calcium homeostasis, which is caused by germline loss-of-function mutations of the calcium-sensing receptor (CaSR) in ~70% of cases. We report a 22 year old woman who was referred with asymptomatic hypercalcaemia. Biochemical investigations revealed hypercalcaemia on 3 of 4 occasions with adjusted serum calcium ranging from 2.59–2.80 mmol/l (normal range 2.20–2.60 mmol/l). Parathyroid hormone levels ranged from 4.2–6.5 pmol/l (normal range 1.6–7.2 pmol/l). Urinary calcium excretion was 3.5 mmol in 24 hours (normal range 2.5–7.5 mmol/24 h). Spot urinary calcium creatinine clearance ratio was calculated at 0.0095 (normal >0.01). Investigations were consistent with a diagnosis of FHH, prompting genetic testing. Molecular analysis of the CaSR gene revealed a novel heterozygous single base pair substitution, Cytosine to Guanine, at nucleotide c.545. This resulted in the substitution of an evolutionarily conserved serine residue for a mutant cysteine residue at position 182 of the CaSR protein. Modelling studies using the crystal structure of the dimeric human CaSR revealed that the wild-type Ser182 residue is located within a densely packed region of the extracellular domain, which is critical for ligand binding and receptor dimerization. The wild-type Ser182 residue was shown to interact with multiple CaSR residues including Gln164, Ile162, and Ala154, whereas the mutant Cys182 residue is predicted to disrupt the interaction with the nearby Ile162 residue and additionally influence other CaSR extracellular domain residues (Tyr161 and Leu461) through effects on Van der Waals interactions. Thus, these studies involving an FHH patient have identified a novel missense mutation, which is predicted to impair the function of the CaSR extracellular domain.

DOI: 10.1530/endoabs.65.OC3.5

OC3.6

The role of biased calcium-sensing receptor signalling in urinary calcium excretion and kidney stone disease

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Nephrolithiasis is a major clinical and economic health burden. We performed a genome-wide association study in British and Japanese nephrolithiasis populations and identified twenty nephrolithiasis-associated loci, five of which (*DGKD, DGKH, WDR72, GPIC1* and *BCR)* were predicted to influence calcium-sensing receptor (CaSR) signalling. Gain-of-function CaSR-signalling pathway mutations cause enhanced signalling via intracellular calcium ($[Ca^{2+}]_i$) and MAPK pathways and result in autosomal dominant hypocalcaemia (ADH), with hypercalciuria, and we hypothesised that these CaSR-related loci may cause enhanced CaSR-signal transduction and an attenuated ADH-phenotype. We have previously reported the *DGKD*-associated locus to correlate with urinary calcium excretion but not serum calcium concentrations, and we therefore investigated the effects of DGKD knockdown on CaSR-signal transduction *in vitro*. MAPK responses of HEK-CaSR-SRE and HEK-CaSR cells, treated with scrambled or *DGKD* targeted siRNA, to alterations in extracellular calcium concentration $[Ca^{2+}]_e$, as assessed by SRE-reporter and ERK-phosphorylation (pERK) assays, respectively, were significantly decreased in DGKD-knockdown cells (DGKD-KD) compared to wildtype (WT) (SRE maximal response DGKD-KD = 5.28 fold change, 95% confidence interval (CI) = 4.77–5.79 vs. WT = 7.20 fold change, 95% CI = 6.46-7.93, $P = 0.0065$, pERK maximal response DGKD-KD = 24.77, 95% CI = 22.16-27.38 vs. WT = 39.46 fold change, 95% CI = 34.07-44.84, $P = 0.0056$). Cinacalcet rectified attenuated SRE responses (DGKD-KD + 5nM cinacalcet, maximal response = 7.62 fold change, 95% CI = 5.98–9.27). However, $[Ca^{2+}]_i$ responses to $[Ca^{2+}]_e$ alterations were unaffected when HEK-CaSR-NFAT and HEK-CaSR cells were treated with scrambled or *DGKD* targeted siRNA and assessed by NFAT-reporter and Fluo-4 calcium assays, respectively. Our results suggest that the *DGKD* increased-risk allele associates with relatively increased DGKD expression that enhances CaSR-mediated signalling via the MAPK pathway but not $[Ca^{2+}]_i$. This biased signalling may provide an explanation for the correlation of the *DGKD*-associated locus with urinary calcium excretion but not serum calcium concentration. Our findings suggest that the development of biased calcilytics may provide a therapeutic approach to reduce urinary calcium excretion in hypercalciuric patients.

DOI: 10.1530/endoabs.65.OC3.6

Thyroid

OC4.1

A high-throughput yellow fluorescent protein (YFP) cell-based screen identifies autophagy modulators to increase the effectiveness of radioiodine therapy

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New targeted drug strategies are urgently needed to improve radioiodine uptake and efficiently ablate thyroid cancer cells thereby minimising the risk of recurrent disease. High-throughput screening (HTS) offers a promising approach to identify new candidate drugs that will induce sodium iodide symporter (NIS) function to promote iodide uptake. However, significant progress has been limited by a lack of thyroid cell-based assays amenable to HTS. Here, we constructed a thyroid cancer cell reporter consisting of a modified version of the yellow fluorescent protein (YFP) as a biosensor of intracellular iodide. We then screened the Prestwick Chemical Library (1200 drugs; 95% approved; 10 mM dose; $n = 2$) with iodide uptake monitored by quenching of YFP fluorescence. Preliminary results showed that the YFP cell-based assay was sensitive towards iodide uptake (Z-factor = 0.82) with cell viability >75% for most drugs (1033/1200; AlamarBlue). Normalization of the primary screen dataset using an interquartile mean well-based method identified 48 hit candidate drugs which increased iodide uptake >2 s.d. above mean. Of particular interest, categorisation of top hits revealed a high proportion of drugs that modulate autophagy (18/48; 37.5%) - a key process for maintaining cellular homeostasis by degrading/recycling intracellular material. Secondary screening confirmed the role of autophagy modulators in enhancing iodide uptake after ranking 73 leading compounds based on their pharmacologic (AUC, E_{MAX} and EC_{50}) and specificity of response (NIS + ve vs. NIS-ve YFP-thyroid cells) at ten different drug doses (0.1–50 μM). Subsequent treatment of primary human thyrocytes with the repurposed drug prestw-138 further demonstrated greater radioiodine (^{125}I) uptake (~3.5-fold; $P < 0.05$). In summary, we have performed high-throughput screening and identified autophagy modulators as well as other repurposed drugs that induce iodide uptake. We propose that these drugs either alone or in combination with existing therapies might offer new therapeutic strategies to improve the treatment of thyroid cancer.

DOI: 10.1530/endoabs.65.OC4.1

OC4.2

Reduced Length of Hospital Stay with the use of recombinant TSH compared to Thyroid Hormone Withdrawal –A two centre retrospective study

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Background
High risk patients with differentiated thyroid cancer (DTC) undergoing radioiodine (I-131) treatment can be prepared by thyroid hormone withdrawal (THW) or with parenteral recombinant TSH (rhTSH). We compared two centres predominantly using THW or rhTSH to study the impact on radioiodine retention and length of hospital stay (LoHS).
Methods
We retrospectively compared radioactivity at discharge following high dose I-131 therapy (3–5 GBq administered activity) between THW (Centre-A) and rhTSH (Centre-B). Baseline characteristics (in a euthyroid state) were obtained from pre-operative records. The creatinine value prior to I-131 therapy was taken for GFR calculation (Pre-radioiodine GFR). The outcome parameters compared were radiation dose emission rate at 1 metre before discharge and LoHS.
Results
We included 57 and 87 patients in THW and rhTSH arm respectively (Table 1). Data are mean (±S.D.) unless otherwise stated. The mean age of the study population was 53 ±17 and 50 ± 15 years in Centre-A and B respectively. Only the important findings are presented here.

Table 1

	Centre-A (THW $N=57$)	Centre-B (rhTSH $N=87$)	P-value
Tumor			0.455
T1 and T2	29%	35%	
T3 and T4	71%	65%	
Baseline eGFR (ml/min)	96.57±18.61	96.15±15.60	0.420
Pre-radioiodine eGFR (ml/min)	74.63±19.74	95.60±16.14	0.0001
LoHS (days)	4.08±0.66	1.68±0.60	0.0001
Percentage meeting target dose rate at discharge (<30 uSv/hour @ 1metre)	98.6%	95.4%	0.247

Conclusion
There was a significant reduction in eGFR between euthyroid and hypothyroid state in THW arm ($P<0.05$) when compared with rhTSH arm (who remain euthyroid during the I-131 therapy). This impairment of renal function in THW arm caused increased I-131 retention and contributed to an increased LOHS (4 days rather than 2). The impact on renal function and LoHS should also be a factor when considering use of rhTSH with shorter LoHS and scope to relax radiation protection guidance earlier.
DOI: 10.1530/endoabs.65.OC4.2

OC4.3

The disturbed thyroid gland homeostasis in conditions of subacute exposure to thyroid-disrupting chemicals: experimental study in Wistar rats

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The potential health threat posed by endocrine-disrupting chemicals has come to the forefront of environmental health in previous years and nowadays represents a major concern among scientific, regulatory and public communities. Different groups of environmental chemicals appear to have thyroid-disrupting properties. The lifelong exposure to these chemicals raises concerns about their deleterious effects on human health, having in mind that even subtle changes in the individual thyroid homeostasis during the life cycle may have significant adverse effects. This experimental study was aimed to assess effects of repeated relatively low doses (corresponding low to high environmental human exposures) of toxic metal cadmium (Cd), and persistent organic pollutants: polychlorinated biphenyls (PCBs), and polybrominated diphenyl ether (BDE 209) on thyroid homeostasis in adult animals. These chemicals were chosen based on their persistency, high toxicity and ubiquitous presence in environment. Rats were randomized into 20 experimental groups: 6 receiving aqueous solution of Cd (doses ranging from 0.3 to 10 mg/kg b.w.), 6 receiving PCBs dissolved in corn oil (0.5–16 mg/kg b.w.), 5 groups receiving BDE 209 dissolved in DMSO (31.25–500 mg/kg b.w.), and vehicle control groups. Treatment of all animals was performed by oral gavage, each day, during 28 days. Thyroid hormones were adversely affected by Cd, with most prominent effect observed on triiodothyroxine (T3) levels. Applied doses of PCBs induced dose dependent decrease in thyroxine levels (T4) while BDE 209 caused increase in T4 and decrease in T3 levels, compared to respective controls. The strong positive correlation between external/applied doses and target tissue content fortified the reliability of the obtained results. The study implicates that exposure to low, environmental doses of these chemicals interferes with thyroid function and raises an issue of their thyroid disruptive properties at levels to which human are exposed on daily bases.
DOI: 10.1530/endoabs.65.OC4.3

OC4.4

Development of auto-immune thyroid dysfunction in multiple sclerosis patients receiving Alemtuzumab is associated with improved response to treatment

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Background
Alemtuzumab is an anti-CD52 monoclonal antibody used in the treatment of relapsing-remitting multiple sclerosis (MS). Between 20 and 40% of Alemtuzumab-treated MS patients develop autoimmune thyroid disease (AITD) as a side effect. It is currently unknown whether development of AITD correlates with MS disease activity following Alemtuzumab treatment.
Aims
To characterise the types and frequency of AITD that MS patients develop following Alemtuzumab treatment. To determine whether MS disease progression following Alemtuzumab treatment differs in in patients that develop AITD, compared to those who do not.
Methods
A retrospective analysis was performed on all MS patients receiving Alemtuzumab (2012–2017) at Imperial College Healthcare NHS Trust. Data were collected on patients who did and did not develop AITD following Alemtuzumab including thyroid function, disability outcomes (Expanded Disability Status Scale, EDSS), relapses and new MRI demyelinating lesions.
Results
One-hundred and twenty-six patients were included in the study analysis (33 AITD and 93 non-AITD). Twenty-six percent of Alemtuzumab-treated MS patients developed AITD, 54.5% of which was Grave's disease. Patients that developed AITD exhibited a reduction in EDSS score following Alemtuzumab compared to those that did not (median [IQR]; AITD: −0.25 [−1 − 0.5] vs. non-AITD: 0 [1 − 0]. $P=0.007$). Multivariate regression analysis confirmed that the development of AITD was independently associated with improvement in EDSS score ($P=0.011$). Moreover, AITD patients had higher relapse-free survival following Alemtuzumab ($P=0.023$). There was no difference in the number of new MRI lesions developed following Alemtuzumab between the two groups.
Conclusion
Graves' disease was the most common form of AITD developed by MS patients following Alemtuzumab. MS patients who develop AITD exhibit a better response to Alemtuzumab, as measured by EDSS score and relapse rate. A large, prospective study to investigate this further is needed.
DOI: 10.1530/endoabs.65.OC4.4

OC4.5

The prevalence of thyroid dysfunction and autoimmunity in women with history of miscarriage or subfertility across the United Kingdom

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Thyroid dysfunction and autoimmunity are associated with adverse fertility and pregnancy outcomes. International bodies recommend routine thyroid function screening in women with history of subfertility or miscarriage. Knowledge about the frequency of, and risk factors for, thyroid disease is limited in the asymptomatic preconception population. A prospective multi-centre study of women with history of miscarriage or subfertility conducted at 49 hospitals across the United Kingdom between 2011 and 2016. Thyroid function tests and anti-thyroid peroxidase antibodies (TPOAb) were recorded in 19 213 and 19 237 women respectively. The overall prevalence of abnormal thyroid function was 4.8% (95% CI 4.5–5.1), with euthyroidism defined as thyroid stimulating hormone (TSH) 0.44–4.50 mIU/l and free thyroxine (fT4) 10–21 pmol/l. Overt hypothyroidism (TSH >4.50 mIU/l and fT4 <10 pmol/l) was present in 0.2% (95% CI 0.1–0.3) and overt hyperthyroidism (TSH <0.44 mIU/l and fT4 >21 pmol/l) in 0.3% (95% CI 0.2–0.3). The prevalence of subclinical hypothyroidism (SCH) using an upper TSH concentration of 4.50 mIU/l was 2.4% (95%CI 2.1–2.6). Lowering the upper TSH limit to 2.50 mIU/l, a commonly adopted practice, resulted in a higher rate of SCH of 19.9% (95%CI 19.3–20.5). Multiple regression analyses found increased odds of SCH (TSH >4.50 mIU/l) with body-mass index (BMI) $\geq$35.0 kg/m^2 (aOR 1.71 (1.13–2.57) $P=0.01$) and Asian ethnicity (aOR 1.76 (1.31–2.37) $P<0.001$), as well as increased odds of SCH (TSH $\geq$2.50 mIU/l) with subfertility (aOR 1.16 (1.04–1.29) $P=0.008$). TPOAb positivity was found in 9.5% (95%CI 9.1-9.9). BMI $\geq$35.0 kg/m^2 and TSH concentrations $\geq$2.50 mIU/l were associated with greater odds of TPOAb positivity. Subclinical hypothyroidism and thyroid autoimmunity are common in women with history of miscarriage or subfertility; particularly in those with higher BMI and in Asian women. Applying a TSH cut-off of 2.5 mIU/l to define SCH results in a significant proportion of women potentially requiring levothyroxine treatment preconception and during pregnancy. The risks and benefits of this treatment strategy need to be evaluated further.

DOI: 10.1530/endoabs.65.OC4.5

OC4.6

Driver events in thyroid cancer recurrence

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Thyroid cancer is increasing in incidence worldwide. While outcomes are generally good, up to 25% of patients suffer recurrence, and this has a significant impact on their quality of life and life expectancy. We hypothesised that thyroid tumours which recur display a distinct pattern of driver events, present on initial histology. Controlled-access TCGA data on thyroid cancer were downloaded and whole exome sequencing data analysed. An analysis pipeline utilising Platypus, Annovar and SIFT/PolyPhen2/MutationTaster filtering was performed in $n=43$ recurrent patients. This identified mutations in genes including Inosine-5 (-monophosphate dehydrogenase 2 (IMPDH2), 6-Phosphofructo-2-Kinase/Fructose-2,6-Biphosphatase 4 (PFKFB4) and Dicer 1 ribonuclease type III (DICER1). In silico analysis suggested these variants to be pathogenic and therefore they were recapitulated using site-directed mutagenesis. Cellular migration, invasion and subcellular localisation were investigated in cell lines representing the most common background driver mutations of papillary thyroid cancer (TPC1 cells (RET/PTC mutation); SW1736 (BRAFV600E); Cal62 (Ras)). IMPDH2 mutation significantly increased cell migration at 4, 8 and 24hrs vs. WT ($P=0.0068$, $P=0.0008$, $P=0.0088$, respectively), and DICER1 mutation induced increased cell migration at 24 h vs. vector-only ($P=0.0094$) in TPC1 cells. An analysis of RNA and microRNA expression levels was performed, comparing recurrent ($n=43$) to non-recurrent ($n=457$) TCGA patients. In the RNA analysis genes involved in matrix adhesion and thyroid cancer pathogenesis were most differentially expressed in recurrent patients, including fibronectin 1 (FN1) and α3 integrin (ITGA3). Overexpression of FN1 increased cell migration (TPC1s $P=0.007$; SW1736s $P=0.0001$; Cal62 $P=0.01$) and knockdown of ITGA3 decreased cell migration at 24 h (TPC1 $P=0.001$ SW1736 $P=0.0003$, Cal62 $P=0.0056$) but not cell proliferation. MicroRNA analysis highlighted miR 221, 486 and 1179 as miRs significantly differentially expressed in recurrence. We propose that altered RNA and miRNA expression levels may be key to predicting thyroid cancer recurrence.

DOI: 10.1530/endoabs.65.OC4.6

Adrenal and Cardiovascular

OC5.1

Central role for corticosteroid-binding globulin in rat HPA axis sexual dimorphism

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Many organs are functionally sexually dimorphic, resulting in profound differences in the activity of several physiological systems, including the hypothalamic-pituitary-adrenal (HPA) axis. The rodent HPA axis matures post-weaning, characterized by parallel increments in adrenal weight, adrenal cortical size and corticosterone secretion. Between postnatal days (PND) 30 to 45, these parameters increase to a greater extent in females compared to males. Over this same interval, hepatic production of corticosteroid-binding globulin (CBG), a plasma protein that regulates the bioavailability of 'free', unbound steroid to tissue, also increases to a greater extent in females. Thus, we postulate that variations in CBG contribute to the sexual dimorphism of the HPA axis. To explore this possibility, we produced a unique rat model in which the *SerpinA6* gene encoding CBG was disrupted using a CRISPR/cas9 strategy and followed the maturation of the HPA axis in both males and females. Relative to wild type controls, adrenal weight was normal at PND 30, but lower at PND 45, 60 and 90 in female knockout (KO) rats; whereas male KO rats showed no such differentiation. This reduction in adrenal size in the female KO rat was reflected by an equally remarkable change in the adrenal transcriptome. Thus, while female KO adrenals responded to show ~3500 differentially expressed genes, virtually no differences were observed between male KO and controls. Free corticosterone levels were comparable in controls and KO animals regardless of sex, but only female KO rats displayed a reduction in total corticosterone levels. We conclude that CBG contributes to the ontogeny of sex differences in the HPA axis; and predict that it may also be responsible for the morphogenesis of other glucocorticoid sensitive organ systems.

DOI: 10.1530/endoabs.65.OC5.1

OC5.2

Subclinical alpha-1 antitrypsin deficiency is associated with increased free cortisol fraction in plasma

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Background
Corticosteroid Binding Globulin (CBG) binds >85% of plasma cortisol and controls the circulating free cortisol pool. Proteolytic cleavage by neutrophil elastase is proposed to reduce CBG binding affinity and increase free cortisol availability to inflamed tissues. The CORtisol NETwork (CORNET) consortium found that genetic variation at a locus spanning *SERPINA1* (encoding alpha-1 antitrypsin, A1AT, the endogenous inhibitor of neutrophil elastase) and

SERPINA6 (CBG) contributes to morning total plasma cortisol variation. We hypothesised that A1AT deficiency increases CBG cleavage and hence free plasma cortisol. We tested this in recall-by-genotype studies of people who are heterozygous for inactivating mutations in *SERPINA1*.

Methods

16 healthy carriers of either of the two most common A1AT-deficiency single nucleotide polymorphisms (rs17580 & rs28929474) and 16 age-, gender- and BMI-matched controls were recruited from the Generation Scotland Biobank. Plasma free cortisol was measured by isotopic dilution and ultrafiltration, total CBG by ELISA in plasma, and A1AT by ELISA in serum.

Results

Serum A1AT was confirmed lower in those with heterozygous mutations vs. wild type controls (411.3 +/− 27.44 vs. 565.1 +/− 23.38 mg/dl, $P=0.0002$). No significant differences in total CBG were observed. However, plasma free cortisol fraction was higher in those carrying A1AT mutations (16.13 +/− 0.2 vs. 13.88 +/− 0.04 %, $P<0.0001$).

Conclusion

Alpha-1 antitrypsin mutation heterozygosity, common in the general population, is associated with higher free cortisol fraction, consistent with enhanced cleavage of CBG. This may influence tissue actions of glucocorticoids and provides a paradigm in which to dissect the pathophysiological importance of CBG cleavage.

DOI: 10.1530/endoabs.65.OC5.2

OC5.3

Common variants in the gene encoding corticosteroid binding globulin influence cortisol-responsive gene networks in human adipose tissue

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A genome wide meta-analysis by the CORtisol NETwork (CORNET) consortium[1] has identified genetic variants spanning the *SERPINA6/SERPINA1* locus on chromosome 14 associated with changes in morning plasma cortisol and predictive of cardiovascular disease (Crawford *et al*, Unpublished). *SERPINA6* encodes Corticosteroid Binding Globin (CBG) which binds most cortisol in blood and influences delivery of cortisol to target tissues. We hypothesised that genetic variants in *SERPINA6* influence CBG expression and cortisol delivery to tissues which promote cardiovascular disease, reflected in tissue-specific variation in cortisol-regulated gene expression.

The Stockholm Tartu Atherosclerosis Reverse Networks Engineering Task study (STARNET)[2] provides genome wide DNA and RNAseq data in 7 vascular and metabolic tissues from patients undergoing coronary artery bypass grafting. We used STARNET to link SNPs identified in CORNET to *SERPINA6* transcript levels and the expression of other trans-associated genes. Causal inference[(3)] was employed to reconstruct interactions between these genetic factors and their downstream targets.

We identified 21 SNPs that were significant in CORNET ($P \leq 5\times10^{-8}$) and cis-eQTLs for *SERPINA6* expression in liver ($q \leq 0.05$). Tissue-specific trans-genes in liver, subcutaneous and visceral abdominal adipose tissue were associated with these SNPs, with over-representation of glucocorticoid-regulated genes. The interferon regulatory trans-gene, *IRF2*, controls a putative glucocorticoid-regulated network with targets including *LDB2* and *LIP1*, both associated with coronary artery disease.

We conclude that variants in the *SERPNIA6/A1* locus mediate their effect on plasma cortisol through variation in CBG expression in liver, and that variation in CBG influences gene expression in extrahepatic tissues through modulating cortisol delivery, notably in adipose tissue. The cortisol-responsive gene networks identified here represent candidate pathways to mediate cardiovascular risk associated with elevated cortisol.

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DOI: 10.1530/endoabs.65.OC5.3

OC5.4

Pre-receptor metabolism and signalling of glucocorticoids between macrophages and fibroblasts

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The glucocorticoid (GC) activating enzyme 11β-HSD1 is potently upregulated within macrophages and synovial fibroblasts of inflamed joints, where it increases therapeutic GC signalling and regulates their anti-inflammatory profiles. Whilst in vitro studies have demonstrated the importance of autocrine signalling in this context, the importance of paracrine signalling remains poorly defined. In this study, we examined the role of 11β-HSD1 in paracrine GC signalling between macrophages and fibroblasts *in vitro*. Conditioned media (CM) and transwell co-culture experiments were set up using fibroblast-like synoviocytes (FLS) and peritoneal macrophages from wild type (WT) or 11β-HSD1 knock-out (KO) mice. CM was generated by stimulating WT or KO macrophages and FLS with the inactive GC dehydrocorticosterone (DHC; 1000 nmol/l) for 24 h. KO FLS or macrophages were then cultured for 24 h with CM. Parallel transwell (0.4 μm) co-cultures were established using the same cell populations. GC responses in CM-treated or co-cultured KO macrophages and FLS were examined by RT-qPCR (Gilz, Il-6, Tnfa) and cytokine secretion measured using ELISA (IL-6). KO FLS significantly upregulated Gilz and suppressed Il-6 expression in response to CM from WT macrophages exposed to inactive DHC (GILZ 4.8 fold increase, Il-6 4.2 fold decrease). These responses were lost with CM from KO macrophages on KO fibroblasts. Similar responses were evident in KO macrophages exposed to CM from WT fibroblasts treated with DHC (Gilz 7.8 fold increase, Il-6 5.6 fold decrease, Tnfa 1.4 fold decrease). Similar results were apparent in co-culture experiments exposed to DHC, where KO macrophages and FLS responded to inactive DHC when cultured with WT but not KO counterparts. Co-culture ELISA data for IL-6 production matched mRNA results. This study demonstrates that 11β-HSD1 can mediate paracrine GC signalling between macrophages and fibroblasts in vitro. These data demonstrate that targeted delivery of GCs to either cell population will likely impact on both in vivo.

DOI: 10.1530/endoabs.65.OC5.4

OC5.5

Somatic transmembrane domain mutations of a cell adhesion molecule, CADM1, cause primary aldosteronism by preventing gap junction communication between adrenocortical cells

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Background

Primary Aldosteronism (PA) is the commonest curable cause of hypertension. Whole exome sequencing (WES) of an aldosterone producing adenoma from a 46-year-old man with resistant hypertension revealed a novel somatic mutation (Val380Asp) of the single transmembrane domain of Cell Adhesion Molecule-1 (CADM1). A Gly379Asp mutation was identified by WES of a PA patient in Munich. Both patients were cured of hypertension by adrenalectomy.

Method

Adrenocortical (H295R) cells were transduced with wild-type (WT) and mutant *CADM1* to assess changes in aldosterone production. Previous studies showed *CADM1* to regulate gap junctions (GJ) in islet cells. This was assessed in H295R cells by dye transfer. The effect of inhibiting GJs was also interrogated. Finally WT or mutant cells were co-transfected with CX-43 tagged by mApple or Venus fluorophores and mixed, allowing confocal visualisation of GJ formation between adjacent cells.

Results

Cells transduced with mutant *CADM1* showed 3-6-fold increase in aldosterone secretion ($P<0.0001$) and 10-20-fold increase in CYP11B2 expression ($P<0.0001$). Transfer of calcein (a GJ-permeable dye) was reduced between

mutant *CADM1* cells, compared to untransfected or WT cells ($P<0.001$). Inhibition of CX-43 caused 2-fold increase in aldosterone secretion, 8-fold (<0.05) increase in CYP11B2 expression. Protein modelling suggested that mutations increased the angle of ectodomains to cell membrane, from 49° in WT, to 62° and 90° in Gly379Asp and Val380Asp respectively, increasing inter-cell distance from 21.2 nm to 24.7 and 27.9 nm. A role of CADM1 may be to bring opposing CX-43 hemichannels close enough to form GJ channels. Mixing of fluorescent-tagged CX-43 cells showed fewer intact GJ channels in *CADM1*-mutant cells.

Conclusion

Discovery of the *CADM1* mutation reaffirms the importance of membrane proteins in aldosterone regulation, although *CADM1's* impact on cation traffic is indirect. The role of cell-adhesion in regulating GJs suggests a role for these in the regulation of aldosterone by oscillating Ca^{2+} currents.

DOI: 10.1530/endoabs.65.OC5.5

OC5.6

SLC35F1, a potential marker for aldosterone producing cell clusters

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Background

Aldosterone producing cell clusters (APCCs) are microscopic pockets of cells in the adrenal zona glomerulosa (ZG), which stain densely for aldosterone synthase (CYP11B2). They exist in 30% of normal adrenal glands and have similar somatic genetic mutations as some aldosterone producing adenomas (APA), especially of *CACNA1D*. Some APCCs are precursors to APAs. Adrenalectomy for primary aldosteronism (PA) cures hypertension in $<$ 50% of patients, maybe because of APCCs in the contralateral gland. A potential surface marker of APCCs is SLC35F1: a mainly neuronal decamembrane-spanning nucleotide sugar transporter. Structural similarity suggests a possible role as nicotinamide transporter, reflecting high NADPH requirements in steroidogenesis. Microarray data demonstrated exquisitely selective upregulation of SLC35F1 mRNA in APCCs, and Wnt-activated APAs (with CTNNB1 mutations), but not in surrounding ZG.

Methods

4μm sections of paraffin embedded normal and para-APA adrenal tissue were stained using Gomez-Sanchez's monoclonal antiserum to CYP11B2 and, on serial sections, of polyclonal anti-SLC35F1 (Novus NBP1-86755). HEK293 cells were transfected with GFP-tagged SLC35F1 to study subcellular localisation, as a prelude to 3H-nicotinamide uptake experiments.

Results

There was strong staining of CYP11B2 in clusters of cells in ZG, consistent with APCCs, in all adrenal glands adjacent to ZG-like APAs ($n=9$) except for 3 adrenals adjacent to CTNNB1-mutant APAs. Serial sections showed exquisite positive staining for SLC35F1 in APCCs, with no staining in surrounding ZG, ZF or ZR. Staining appeared membranous, but in transfected HEK293 cells was more variable.

Conclusions

SLC35F1 is abundantly and selectively expressed in APCCs. Recent studies in other cell-types have suggested endosomal shuttling of SLC35F1, possibly consistent with our findings in transfected cells. Localisation to plasma membrane in APCCs would enable antibody separation of APCC cells from primary adrenal cultures and provide a target for novel therapies which selectively inhibit autonomous aldosterone production. Its functional role is now under investigation.

DOI: 10.1530/endoabs.65.OC5.6

Reproductive Endocrinology and Biology

OC6.1

Effect of MVT-602, a potent kisspeptin receptor agonist, on LH levels in healthy pre-menopausal women undergoing a minimal controlled ovarian stimulation protocol

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Background

Kisspeptin is an endogenous neuropeptide that regulates GnRH release from the hypothalamus. Kisspeptin-54 has been shown to effectively trigger oocyte maturation during in vitro fertilisation (IVF) treatment, but with markedly reduced rates of ovarian hyperstimulation syndrome (OHSS). The kisspeptin receptor agonist, MVT-602, has a longer half-life than native kisspeptin-54 (1.5–2.2 h vs. 0.5 h) and has potential for development as a novel trigger of oocyte maturation. LH concentrations following kisspeptin-54 are augmented during controlled ovarian stimulation (COS); thus we investigated the LH-profile of MVT-602 in the context of a minimal COS protocol.

Methods

A randomised, double-blind, placebo and active comparator-controlled, phase 2a study was conducted (May-October 2018). Seventy-five healthy women (aged <36 years, BMI 18–30 kg/m^2) underwent minimal COS (recombinant FSH / GnRH antagonist). Once the dominant follicle reached ≥ 17 mm, women were randomised to receive a single subcutaneous dose of MVT-602 (0.1, 0.3, 1.0 or 3.0 μg; $n=16$-17 per group), GnRH agonist triptorelin 0.2 mg ($n=5$), or placebo ($n=5$) in a 3:1:1 ratio. Hormone levels were monitored every 2–4 h for 48 h and then daily for 13 days, or until ovulation was confirmed.

Results

MVT-602 induced an LH surge that peaked at 16–24 h to ~50 IU/l and provided LH-exposure for more than 48 h. Doses of MVT-602 of 0.3 mcg or greater increased LH sooner and with greater consistency. The proportion of women who ovulated within 5 days of trigger administration increased with dose of MVT-602 (Placebo 60%, 0.1 μg 75%, 0.3 μg 82%, 1 μg 88%, 3 μg 100%). LH-rise after GnRH agonist was more pronounced (peak LH >150 IU/l) and occurred sooner (~4 h) than following MVT-602.

Conclusion

The LH-profile following MVT-602 more closely mirrored that of the natural mid-cycle LH surge providing LH-exposure for >48 h. Thus, MVT-602 could offer an advantageous profile in the triggering of oocyte maturation during IVF treatment.

Trial registration number: 2018-001379-20

DOI: 10.1530/endoabs.65.OC6.1

OC6.2

Differential follicle stimulating hormone glycosylation modulates follicle growth and survival rates

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Ovarian aging is a naturally occurring physiological process, marked by dynamic changes in ovarian function and hormone secretion. Ovarian ageing is associated with several co-morbidities, including; osteoporosis, diabetes, cardiovascular disease and impaired cognitive function, therefore, understanding the physiological processes regulating this is imperative for identifying novel treatment modalities. A key endocrine regulatory of ovarian function is the heterodimer glycoprotein hormone, follicle stimulating hormone (FSH). FSH is secreted as two glycosylation variants; partially glycosylated FSH (FSH21) and fully glycosylated FSH (FSH24). These variants have different bioactivities, FSH21 is more biologically active than FSH24. Interestingly, the ratio of FSH21:FSH24 changes with age, with FSH21 predominant in women of reproductive prime, and FSH24 predominant in menopausal women. Yet, if these FSH glycosylation variants differentially modulate follicle growth and survival remains unknown. This study aimed to determine the effects of FSH21 and FSH24 on follicle growth and survival. To do this, mouse ovarian follicles were isolated from 3-4wk-old-C57/BL6 mice and treated +/− 10 ng/ml, FSH21($n=31$), FSH24($n=30$), a ratio of 80:20 FSH21:FSH24 (to mimic reproductive prime; $n=32$) or 20:80 FSH21:FSH24 (to mimic late peri-menopause; $n=22$). Follicles were cultured for up to 96hrs and imaged daily to evaluate follicle morphology. Follicle growth was markedly increased at 48, 72, and 96 h time points, when cultured in the presence of FSH21 or 80:20 FSH21:FSH24, in comparison to control, FSH24 alone and 20:80 FSH21:FSH24 conditions. Follicles treated with FSH24 or 20:80 FSH21:FSH24 tended to undergo basement membrane rupture and oocyte extrusion. Moreover, survival rates were significantly increased in follicles treated with FSH21 or 80:20 FSH21:FSH24. These data suggest that the nature of FSH glycosylation modulates the follicular cellular environment to regulate follicle growth and survival. These findings have important implications for IVF

ovarian hyperstimulation treatment regimens. Moreover, the ratio of FSH21:FSH24 may be an important novel biomarker of ovarian ageing.

DOI: 10.1530/endoabs.65.OC6.2

OC6.3

Investigating the impact of altered maternal extracellular vesicle miRNAs on placental function in women with gestational diabetes complicated by large for gestational age infants

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Gestational diabetes mellitus (GDM) increases fetal morbidity/mortality, and is associated with elevated risks of offspring cardiometabolic disease. These risks are compounded in infants born large for gestational age (LGA) rather than appropriate size (AGA), a common complication of GDM associated with altered placental function. Circulating extracellular vesicle (EV)-associated miRNAs are internalised into the placenta and are emerging as key GDM mediators, with their role in LGA yet to be explored. We hypothesise that maternal EV-miRNAs may alter placental function in concurrent GDM-LGA. Serum was collected from GDM women (26–28 weeks). Birth outcomes and placental tissue were collected at delivery. EV-associated miRNAs were profiled using qPCR arrays ($n=7$) which showed that miR-200c-3p (2.78-fold; $P<0.05$ vs. AGA) and miR-375 (4.74-fold; $P<0.01$ vs. AGA) were elevated in the sera of GDM women with LGA infants and in the placentas of a separate cohort ($P<0.05$ vs. AGA; qPCR). Gene ontology enrichment analysis identified that predicted targets (e.g. insulin-like growth factor receptor-1 (IGF1R), a key regulator of placental proliferation) of these miRNAs are central to placental metabolism/development. To functionally confirm these predictions, miR-200c-3p and miR-375 were over-expressed in the placental BeWo cell-line (miR-200c-3p 8000-fold, $P<0.05$; miR-375 13-fold, $P<0.05$; $n=4$) or normal human term placental explants (miR-200c-3p 9-fold, $P<0.05$; miR-375 30-fold, $P<0.05$; $n=3$) by transfecting with specific miRNA-mimics or non-targeting control (NT; 100 nM; 73 h). The percentage of proliferative $Ki67^{+ve}$ BeWo cells (fluorescence immunocyto-chemistry) was reduced by miR-200c (-17%; $P<0.01$ vs. NT) and miR-375 (-19%; $P<0.05$ vs. NT) transfection ($n=10$). Preliminary Western blot data indicates a trend towards decreased IGF1R in placental explants overexpressing miR-375 (56% reduction vs. NT; $n=3$). These data demonstrate that miR-200c-3p and miR-375 – miRNAs elevated with concurrent GDM and LGA in maternal serum/placenta with concurrent GDM-LGA – alter placental proliferation, potentially linking maternal serum components to fetal growth in GDM.

DOI: 10.1530/endoabs.65.OC6.3

OC6.4

Kallmann syndrome-associated WDR11 regulates primordial germ cell development

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The primary cilium, a non-motile microtubule-based organelle protruding from most vertebrate cells, serves as a specialized compartment for signal transduction. Any disruption of ciliogenesis leads to ciliopathy-spectrum disorder with multiple signalling failure in development and homeostasis. Several ciliopathies including Bardet–Biedl syndrome associate with infertility and hormone imbalances, but the role of primary cilia in reproductive disorders is not clear. Congenital hypogonadotropic hypogonadism (CHH) and Kallmann syndrome (KS) are genetic disorders defined by delayed/arrested puberty and infertility. We previously identified WD-repeat protein 11 (WDR11) was mutated in CHH/KS. Our recent studies demonstrated that WDR11 is required for ciliogenesis and Hedgehog (Hh) signalling. Animal models lacking WDR11 exhibit defective cilia and dysregulation of the Hh signal pathway. This places KS/CHH in the human ciliopathy spectrum. Our current study further demonstrates that the reduced fertility of WDR11-deficient individuals may be due to the defective migration of the pluripotent primordial germ cells (PGCs), resulting in a reduced number of germ cells present in the gonads at birth. PGCs are the founders of gametes. During early gonadogenesis, PGCs migrate towards the developing genital ridges where they integrate with the surrounding mesenchyme before undergoing sex differentiation. By live-imaging of mouse embryo slice cultures, we confirmed the loss of Wdr11 caused a reduced migration capacity of PGCs without affecting their directionality. Hh signalling agonist/antagonist could alter PGC motility. Interestingly, despite their sensitivity to Hh signalling, PGCs are naturally un-ciliated. The somatic cells surrounding the PGCs are widely ciliated, suggesting that the soma may provide the key signals important for PGC migration. Our work has identified the PGC migration defects as one of the underlying causes of KS/IHH, implicating a scenario of primary hypogonadism. Based on these findings, consideration of differential diagnosis and treatment regime can be established for gonadotrophin non-responders.

DOI: 10.1530/endoabs.65.OC6.4

OC6.5

Placental expression of estrogen related receptor γ (ERRγ) is hypoxia-sensitive and is altered in pregnancies complicated by fetal growth restriction

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Fetal growth restriction (FGR) defines a fetus which does not achieve its intrauterine growth potential. FGR is linked to placental dysfunction and hypoxia and is associated with a high risk of stillbirth, neonatal death and long-term complications; there are no treatments. Estrogen related receptor γ (ERRγ) is a nuclear receptor that is regulated by hypoxia in other systems; it is expressed in the placenta, thus we propose that it may be an important regulator of hypoxia-mediated placental dysfunction in FGR pregnancies. Placentas were collected from women delivering appropriate for gestational age (AGA; $n=9$) or FGR ($n=9$) babies, following informed consent. AGA placentas ($n=8$) were dissected and explants cultured for up to 4 days under normoxic (20%) or hypoxic (1%) conditions, or with cobalt chloride ($CoCl_2$; 200 μM), a chemical inducer of hypoxia. hCG and LDH secretion were assessed by ELISA, as a proxy measure of placental cell proliferation and apoptosis. RT-PCR and western blotting assessed mRNA and protein levels of ERRγ in FGR, AGA and cultured explant tissues. Localization of ERRγ in placental tissue was studied by immunohistochemistry. ERRγ was predominantly localized to the maternal-facing syncytiotrophoblast layer of the placenta. ERRγ mRNA ($n=9$; $P=0.02$) and protein expression ($n=10$; $P=0.01$) were significantly decreased in FGR placentas. Both hypoxia and $CoCl_2$ exposure dramatically decreased ERRγ mRNA expression ($n=8$; $P=0.004$ (hypoxia vs. control); $P=0.02$ (CoCl2 vs. control)) but not protein, significantly reduced expression of key signaling molecules downstream of ERRγ, including17β-hydroxysteroid dehydrogenase type 1 (HSD17B1), 11β-hydroxysteroid dehydrogenase type 2 (HSD11B2), cytochrome P-450 (CYP19A1), and placenta specific-1 (PLAC1) ($n=7$; P value <0.05), and significantly reduced hCG secretion and increased LDH ($n=6$; $P=0.03$). These data demonstrate that ERRγ is a hypoxia-sensitive receptor in the placenta and suggests that altered ERRγ-mediated signalling may contribute to hypoxia-induced placental dysfunction in FGR.

DOI: 10.1530/endoabs.65.OC6.5

OC6.6

Kisspeptin enhances the brain processing of attraction in men

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Background
Successful reproduction relies on integration of sensory cues of attraction with corresponding emotions and behaviours. However, the intrinsic factors integrating these fundamental aspects of human attraction with limbic and reproductive pathways have not been fully identified. Kisspeptin is a crucial activator of the reproductive axis and together with its receptor is widely expressed throughout the limbic and olfactory systems in humans suggesting a potential role in this integration. We therefore hypothesised that kisspeptin modulates brain responses to olfactory and visual cues of attraction in men.
Methods
To test our hypothesis, we utilised fMRI to examine the effects of kisspeptin versus placebo on brain activity during olfactory and facial attractiveness tasks in 33 healthy heterosexual men (age 24.5 ± 0.7 years, BMI 22.9 ± 0.8 kg/m^2). During the olfactory task, participants received a pleasant feminine scent and during the facial attractiveness task they viewed unfamiliar female faces. Psychometric and hormone analyses were also performed.
Results
Kisspeptin enhanced brain activity in olfactory ($P < 0.01$) and limbic behavioural circuits ($P < 0.05$), in response to a pleasant feminine scent. On viewing female faces, kisspeptin augmented brain activity in established areas associated with the evaluation of beauty ($P < 0.01$). Additionally, we observed correlations between the effects of kisspeptin on brain activity and psychometric parameters of reward ($P < 0.01$). Of particular translational relevance, the effects of kisspeptin were more pronounced in men reporting lower sexual quality of life ($P < 0.01$), suggesting that kisspeptin-mediated pathways may provide therapeutic avenues for patients with psychosexual disorders.
Conclusion
Collectively, we demonstrate for the first time that kisspeptin enhances brain responses to olfactory and visual cues of attraction with key correlations to psychometric parameters providing functional relevance. Our data provide a novel framework for understanding hormones and human attraction, while also laying the foundations for future therapeutic applications of kisspeptin in associated reproductive and psychosexual disorders.

DOI: 10.1530/endoabs.65.OC6.6

Oral Poster Presentations

Adrenal and Cardiovascular

OP1.1

Betamethasone/GR ChIP-Seq analysis defines a discrete set of canonical GR homodimer binding sites in primary fetal rat lung mesenchymal fibroblasts

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Development of a functional human lung requires regulation of cell growth, proliferation and differentiation in specific germ layer compartments. Important endocrine regulators of respiratory development include glucocorticoid (GC) steroids and the potent synthetic GC betamethasone is commonly used antenatally to treat the deficits of very preterm human birth. Previous studies with conditional mouse knockouts of the glucocorticoid receptor (GR) gene have established the mesenchymal compartment of the lung as the critical target for GC/GR signalling. To identify the direct betamethasone induced GR binding sites in the genome and associated potential gene targets we have stimulated primary cell cultures of fetal rat lung mesenchymal fibroblasts for six hours with betamethasone and analysed cellular responses using GR-ChIP-Seq and RNA-Seq analysis. Strikingly, betamethasone stimulated a much stronger transcriptional response compared to corticosterone. Whole genome betamethasone/GR ChIP-seq analysis identified approximately 165 GR-binding sites across the genome, with nearly all containing a highly conserved canonical 15 bp glucocorticoid response element (GRE) sequence. GREs were located near previously characterised GR-targets genes such as Per1, Sgk1, Fkbp5 and Dusp1, near many GC-induced genes identified with RNA-Seq, and also near many novel genes, that also included non-protein coding miRNA and lincRNA genes. One of the strongest induced genes at the mRNA level was a transcription factor called Zbtb16 whose mRNA levels were induced 60 fold in fetal lung fibroblasts by betamethasone, and two GREs (AGAACACACTGTACC/GGTACACTCTGTACT) were identified in intron B, 80-90kb downstream of the TSS of the Zbtb16 gene. Analysis in the lung of conditional GR-deficient mice showed markedly reduced expression of Zbtb16 in both complete GR-null and lung mesenchymal-GR-deficient mice. These results demonstrate that glucocorticoids induce higher levels and activity of specific cell regulatory pathways in the fetal lung by controlling cell signalling networks to ultimately contribute to the normal program of lung development.

DOI: 10.1530/endoabs.65.OP1.1

OP1.2

Glucocorticoids promote mitochondrial fatty acid oxidation in the fetal heart

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Background
The late gestational surge in glucocorticoids is vital for the maturation of fetal organs in preparation for birth and survival during the neonatal period. Metabolic maturation of cardiomyocytes involves a switch in fuel substrate from glucose utilization to fatty acid (FA) oxidation. In fetal cardiomyocytes, glucocorticoids induce expression of *Ppargc1a* (encoding PGC1a, a master regulator of mitochondrial capacity). We hypothesized that glucocorticoids promote the metabolic switch to FA oxidation during cardiomyocyte maturation.
Methods
Isolated embryonic day 14.5–15.5 mouse C57Bl/6 fetal cardiomyocytes were pre-treated with the glucocorticoid receptor antagonist RU486, or vehicle for 30mins prior to treatment with dexamethasone (dex) or vehicle for 24 h. A Seahorse XF Analyzer was used to measure glycolysis and mitochondrial respiration. Palmitate was used to measure FA oxidation; with etomoxir to block mitochondrial FA uptake. RNA was extracted from cardiomyocytes following 24 h dex or vehicle treatment and from C57Bl/6 E14.5 fetal hearts collected from pregnant dams injected (i.p.) at E13.5 with dex or vehicle. Genes involved in FA oxidation were analysed by qRT-PCR.
Results
Fetal cardiomyocytes exhibited little dependence on glycolysis and this was unaltered by dex treatment. With palmitate, dex treatment increased the basal respiration rate (518 ± 48 vs. 367 ± 71 pmol/min/protein, mean ± S.D., $n = 5$) and oxygen consumption (a measure of ATP production, 160 ± 63 vs. 298 ± 36 pmol/min/protein, mean ± S.D., $n = 5$) compared to vehicle. Etomoxir and RU486 inhibited these dex-dependent increases. In fetal cardiomyocytes, dex increased the expression of genes involved in FA uptake (*Cd36*, *Cpt1a, Cpt1b*) and utilisation (*Lcad, Mcad, Lipin1, Ppargca1)* but not *Sirt1* (involved in autophagy) and *Scad* (short chain FA utilisation). Analysis of genes regulated *in vivo* is underway.
Conclusions
These data support a glucocorticoid-induced switch in substrate preference towards FA oxidation in fetal cardiomyocytes. The mechanism involves upregulation of genes involved in mitochondrial capacity and FA oxidation.

DOI: 10.1530/endoabs.65.OP1.2

OP1.3

Combining 11C-metomidate PET/CT and 18F-FDG PET/CT – a new approach to phenotyping indeterminate adrenal lesions

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Background
^{11}C-Metomidate (MTO)-PET/CT has recently found utility as an alternative to adrenal vein sampling for lateralisation in primary aldosteronism. MTO binds with high affinity to 11b-hydroxylase (*CYP11B1*) and aldosterone synthase (*CYP11B2*) and can be considered an adrenocortical-specific tracer. We and others have therefore hypothesised that combining MTO-PET/CT with ^{18}F-FDG(FDG)-PET/CT would permit indeterminate adrenal lesions to be categorised in terms of (i) adrenocortical origin (MTO positive) or not (MTO negative) and (ii) malignant potential (as determined by extent of FDG positivity).
Method
Eight patients (4 male, 4 female) with a new indeterminate adrenal lesion were investigated using MTO-PET/CT and FDG-PET/CT (single centre, 2015–2019). Intensity and distribution of tracer uptake was independently assessed by two radiologists. Histological confirmation of the adrenal lesion was available for six patients.
Results
Benign and malignant lesions of adrenocortical and non-adrenocortical origin were correctly identified using dual PET studies. MTO uptake was only seen in lesions of adrenocortical origin, whereas high level FDG uptake reliably identified malignant lesions (Table 1).

Table 1

Patient	1	2	3	4	5	6	7	8
Side of lesion	Left	Left	Right	Right	Right	Left	Right	Right
Metomidate uptake	Positive	Negative	Positive	Negative	Negative	Negative	Negative	Negative
FDG uptake	Low	Low	High	High	High	High	High	High
Category	AdC	Non-AdC	AdC	Non-AdC	Non-AdC	Non-AdC	Non-AdC	Non-AdC
	Benign	Benign	Malignant	Malignant	Malignant	Malignant	Malignant	Malignant
Diagnosis	ACA*	GN	ACC	Adrenal Met*	Phaeo[1]	Lymphoma	Lymphoma	Lymphoma

Key: ACA, adrenocortical adenoma; ACC, adrenocortical carcinoma; AdC, adrenocortical; FDG, 18F-FDG; GN, ganglioneuroma; Met, metastasis; MTO, 11C-metomidate; Phaeo, phaeochromocytoma; *histological confirmation of diagnosis not available; [1] patient with normal normetanephrine and borderline raised metanephrines levels.

Conclusion
In this proof-of-concept study MTO- and FDG-PET-CT reliably distinguished between benign from malignant, and adrenocortical from non-adrenocortical, lesions. Further studies are required to confirm these findings.

DOI: 10.1530/endoabs.65.OP1.3

OP1.4

Global phosphoproteomics links rapidly induced cytoplasmic signals to transcriptional control

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Glucocorticoids (Gc) are potent anti-inflammatory steroids which mediate their effects by binding the glucocorticoid receptor (GR). Following ligand binding, GR initiates rapid 'non-genomic' kinase signals in the cytoplasm, then translocates into the nucleus to mediate 'genomic' effects by binding DNA directly or tethering to other DNA bound transcription factors to modulate target gene expression. Little is known about how rapidly induced cytoplasm derived Gc signals might feed forward to modulate the transcriptional response. We have completed global phosphoproteomics following acute (10 min) treatment with three different GR ligands to identify rapidly induced, Gc controlled pathways. In total we identify over 150 Gc regulated phosphoproteins. Of these, we find more than 100 proteins that are controlled by all three GR modulators – suggesting a common signature of GR activation. The identified phosphotargets includes proteins with diverse functions that are localised to the plasma, ER and mitochondrial membranes, the cytoplasm and nucleus. Consistent with our previously published work, we identify phosphoregulation of the lipid raft marker caveolin-1, and the three caveolin partner proteins, cavins 1, 2 and 3. We also identify differential phosphorylation of two G protein coupled receptors which localise to caveolae, thereby linking GR activation with kinase coupled pathways. Functional ontology analysis identifies cyclin-dependent kinase/cyclin mediated phosphorylation of RNA Polymerase II as a key effector pathway following Gc treatment. Using phospho-specific antibodies we demonstrate by immunoblot that the serine phosphorylation signature of Rbp1 C-terminal domain is altered following acute Dex treatment which suggests that rapid Gc signals prime the transcription machinery. We also identify Gc dependent phosphorylation of a number of chromatin re-modellers and transcription factors important for transcription initiation. Collectively our data suggests a common GR-mediated mechanism, whereby rapidly induced Gc signals feed-forward into the nucleus to modulate genomic signals, providing further insight into Gc action *in vivo*.

DOI: 10.1530/endoabs.65.OP1.4

Thyroid

OP2.1

Day case radio-iodine for remnant ablation in differentiated thyroid cancer patients is safe and helps reduce bed pressures in a busy tertiary centre hospital

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The amount of radioactivity given to patients undergoing ablation for remnant tissue in thyroid cancer at our centre has been greatly reduced to 1100 MBq I-131 in recent years, prompting a review of practice. An extensive risk assessment, focusing particularly on radiation exposure to the public during the patient's commute home was conducted and found patients could now be discharged safely on the day of treatment. Owing to these findings and audit showing 86% of patients waited for at least 3 h and 29% were waiting beyond 1700 for bed availability for inpatient treatment, with a knock-on late discharge the following day, we moved to day case treatment in a carefully selected group; eliminating the need for hospital admission and improving waiting times. Currently, all patients meet with the ARSAC license holder and a nuclear medicine physicist prior to being scheduled for their ablation. After a rigorous risk assessment by the nuclear medicine physicist confirming the patient's ability to comply with the necessary restrictions, the patient is consented and given dates to attend for thyrogen administration, blood tests (+/− a pregnancy test), treatment and post-therapy imaging. Only patients who are unable to comply with the precautions are admitted for therapy. Between May 2018 and June 2019, we administered ablation dose to fifty-three patients; twenty (37%) were discharged home the same day, without any reported adverse events. This equates to ~£14 000 in admission saving (estimated admission cost £340) and the equivalent number of bed nights on a busy oncology ward. Other benefits include approximately 4 physicist hours saved, increased bed availability and an anticipated improved patient experience. Retrospective analysis of our data suggests we could double the number of day case treatments through education of the wider team. We plan to collect more patient feedback and continue to expand our practice.

DOI: 10.1530/endoabs.65.OP2.1

OP2.2

The SH2B3 tryptophan 262 variant is associated with Graves' disease and Addison's disease

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Objective
The *SH2B3* gene encodes the src homology-2B adaptor protein 3, also known as lymphocyte adaptor protein (LNK), and is a negative regulator of T lymphocyte activation and the cytokine signalling pathways involved in inflammation and haematopoiesis. *rs3184504*, a non-synonymous SNP (R262W) in exon 3 of the *SH2B3* gene, has been associated with numerous autoimmune conditions including type 1 diabetes, rheumatoid arthritis and coeliac disease. The overlap of risk alleles across multiple autoimmune diseases is a well-recognised phenomenon. This study aims to investigate the role of the *rs3184504 SH2B3* variant in susceptibility to Graves' disease (GD) and autoimmune Addison's disease (AAD).
Design and methods
A case-control association analysis was performed in 687 GD and 420 AAD patients. Samples were genotyped by allele discrimination TaqMan PCR and genotype frequencies compared to 5154 healthy controls from the Wellcome Trust case-control consortium (WTCCC2).
Results
The TT genotype was present in 1210 of the 5154 (23.5%) controls, compared to 196 of 687 (28.5%) GD patients ($P=0.0036$) and 119 of 420 (28.3%) in the AAD cohort ($P=0.026$), using a recessive model. There was no significant difference in the T allele frequency between the GD patients and controls (47.1% in Graves' vs. 48.9% in controls; $P=0.123$), however the T allele was over-represented in AAD patients compared to controls (53.0% vs. 48.9%; $P=0.025$).
Conclusion
Our study shows for the first time that homozygous carriage of the *SH2B3* codon 262 tryptophan allele has a role in the genetic susceptibility to both GD and AAD. Although the function of this SNP has yet to be elucidated in detail, the dysregulation in signalling pathways involving lymphocyte homeostasis may broadly predispose to disease development. Further work is necessary to define the exact mechanism by which this allele contributes to autoimmune disease susceptibility.

DOI: 10.1530/endoabs.65.OP2.2

OP2.3

Sustained improvements in monitoring and biochemical control of hypothyroidism in primary care with the use of an electronic protocol at two year follow up

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Introduction
Thyroid hormone replacement is frequently suboptimal but interventions that are proven to optimise therapy are lacking. In 2017, we developed in EMIS an electronic Protocol for Monitoring Patients on Thyroxine in General Practice ('e-Prompt GP'), to offer automated alerts to prompt GP's to test and address out of range thyroid function tests in patients with hypothyroidism.
Aim
To investigate the long-term impact of an electronic protocol on the monitoring and management of levothyroxine replacement in patients treated for primary hypothyroidism in primary care.
Methods
Five GP practices with a total population of 74,511 patients participated in this study. The prevalence of hypothyroidism was 3.3% and did not change significantly over the course of the study. We audited the percentage of patients who (i) had TSH checked in the preceding 12 months and (ii) had latest TSH level within the local laboratory reference range (0.35–5.0 mU/l) at baseline and at 12 and 24 months after introduction of the 'e-Prompt GP' alerts.

Results
The proportion of patients with TSH checked in previous 12 months increased from 77% to 82% and 83% at 12 and 24 months respectively. The latest TSH was within local reference range in 68% (before) and 72% at both 12 and 24 months following introduction of the 'e-Prompt GP' alerts. The proportion of patients with TSH both within range and checked in last 12 months improved from 53% to 59% after 12 months and remained unchanged at 24 months.
Conclusions
An electronic protocol which prompts GP's to check thyroid function in patients with treated hypothyroidism and alerts them to TSH values that are out of range resulted in improvements which were sustained after 24 months of implementation. Further studies are needed to determine what other measures may be required to achieve further progress in optimisation of thyroid hormone replacement.

DOI: 10.1530/endoabs.65.OP2.3

OP2.4

The proto-oncogene PBF mediates Src modulation of radioiodine uptake

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Successful responses to radioiodine treatment in differentiated thyroid cancer ultimately depend on uptake via the sodium-iodide symporter (NIS). However, many tumors exhibit NIS dysregulation, resulting in a poorer prognosis. Since breast cancer can also overexpress NIS, albeit of limited function, radioiodine treatment may be a promising treatment option. Our previous data show that overexpression of the pituitary tumor-transforming gene-binding factor (PBF) is partially responsible for the reduced function of NIS in thyroid and breast cancer. PBF interaction with NIS leads to reduced NIS plasma membrane localization, decreasing functionality. NIS binding requires a C-terminal PBF tyrosine residue 174 (Y174) to be phosphorylated by the protein kinase Src and hence radioiodine uptake can be modified by Src overexpression and inhibition. To address the mechanistic interactions between NIS, PBF and Src we used CRISPR/Cas9 to knock PBF out in Nthy-ori 3-1 normal thyroid and TPC1 thyroid cancer cells, as well as in MDA-MB-231 and MCF7 breast cancer cell lines. Endonuclease screening, Western blotting and DNA sequencing identified successful PBF knock out (PBF-KO) with at least two different guide RNAs (gRNA). Src overexpression in parental TPC1, MDA-MB-231 and MCF7 cells expressing exogenous NIS significantly repressed radioiodine uptake. In contrast, radioiodine uptake was not altered with Src overexpression in the PBF-KO cell lines. Interestingly Src overexpression had no effect on radioiodine uptake in the Nthy-ori cells. In an alternative approach we previously targeted Src myristoylation and demonstrated increased radioiodine uptake with an N-myristoyltransferase inhibitor. We now show that NMTi significantly induced radioiodine uptake in TPC1 and Nthy-ori parental cells but had no effect in PBF-KO cells. Thus, it is likely that the ability of Src to repress NIS function is dependent on PBF. So, Src inhibitors may contribute to the restoration of radioiodine uptake in thyroid cancer and the utilization of radioiodine in breast tumors.

DOI: 10.1530/endoabs.65.OP2.4

Metabolism and Obesity

OP3.1

Intermittent cold exposure ameliorates fatty liver disease

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Background
Non-alcoholic fatty liver disease (NAFLD) is now the most common liver disease in children and young people. NAFLD can progress to cirrhosis and is associated with cardiometabolic morbidity and mortality, often requiring liver transplant. Brown adipose tissue (BAT) expends energy for thermogenesis when activated by pharmacological agents, e.g. β3-adrenergic receptor agonists, or environmental signals such as cold exposure. We hypothesise that intermittent cold exposure (ICE), unlike persistent cold exposure, is clinically a feasible, non-invasive intervention which could be used alongside conventional therapies for NAFLD and associated cardiometabolic risk factors.
Methods
C57BL/6 mice were fed normal chow (NC) or a high-fat diet for 6 weeks until the mice were confirmed diet-induced obese (DIO) by significant weight gain and glucose intolerance. Mice were then exposed to 6°C for 3 hours over 4 consecutive days or housed at normal laboratory temperature (21°C) and sacrificed 24 h following the last cold exposure. Serum and hepatic lipid biochemistry were measured, alongside hepatic lipid droplet size and expression of fatty acid metabolism enzymes in BAT and liver.
Results
ICE significantly improves obesity and fatty liver disease markers in DIO mice. ICE reduced DIO mouse body weight and normalized liver weight relative to those housed at normal laboratory temperature (21°C). ICE significantly reduced hepatic lipid droplet content in DIO mice by 47%, including a 49% reduction in free fatty acid concentrations ($P < 0.05$), to levels comparable to NC mice. These changes correlated with a 2-fold increase in protein expression of BAT mitochondrial fatty acid oxidation enzyme, hydroxyacyl-CoA dehydrogenase ($P < 0.001$), whereas no change was observed in hepatic expression ($P = 0.15$).
Conclusion
This study demonstrates that in a mouse model, ICE is a feasible intervention to improve steatosis and associated metabolic markers of fatty liver disease through upregulation of BAT-mediated metabolism of lipids.

DOI: 10.1530/endoabs.65.OP3.1

OP3.2

Intestinal injury and evidence of increased gut permeability in female AKR1D1 knockout mice

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Disruption of the gut-liver axis contributes to metabolic syndrome and the progression of non-alcoholic fatty liver disease (NAFLD). Bile acids (BAs) are potent antimicrobials that support gastrointestinal health and dysregulation of BA homeostasis in NAFLD is thought to contribute to gut dysbiosis. Furthermore, an increase in hydrophobic (cytotoxic) BA species may directly affect gut health. We have previously shown that bile acid synthesis enzyme, 5β-reductase (AKR1D1), is downregulated in NAFLD patients. Here we demonstrate the impact of AKR1D1 deletion on intestinal health in female mice. Female wildtype (WT) and AKR1D1-Knockout (KO) mice were maintained on a control diet until 52-weeks of age. Fecal BAs were reduced (WT 2.56 ± 0.49; KO 1.35 ± 0.28 pmol/ng, $P < 0.05$) and LC-MS/MS analysis of serum BAs showed increased hydrophobicity of BA pool (hydrophobicity index: WT -54.9 ± 8.3; KO -23.6 ± 7.1, $P < 4*10\text{-}4$). Although there was no change in total caecal bacterial counts, bacterial composition was altered, with changes seen for species associated with inflammatory status, *Alkaliphilus crotonatoxidans* (WT 0.6%; KO 1.2%, $P < 5*10\text{-}5$) and *Mucispirillum schaedleri* (WT 6.5%; KO 3.7%, $P < 1*10\text{-}6$). Consistent with ileum damage, KOs had decreased villi length (WT 275 ± 11; KO 227 ± 15 um, $P < 0.05$) and increased crypt depth (WT 61 ± 4; KO 71 ± 2 um, $P < 0.05$) as well as increased DNA damage (TUNEL). Key tight junction genes, ZO-1 (WT 0.88 ± 0.05; KO 0.64 ± 0.04, $P < 0.005$), claudin-1 (WT 0.17 ± 0.02; KO 0.09 ± 0.01, $P < 0.05$) and occludin (WT 0.66 ± 0.05; KO 0.38 ± 0.03, $P < 1*10\text{-}4$) were downregulated in ileum, suggestive of increased intestinal permeability. Endorsing our intestinal data, toll-like receptor (TLR4) expression was increased in the liver (WT 0.39 ± 0.01; KO 0.45 ± 0.02, $P < 0.05$). Our results strongly propose that AKR1D1 deletion and disruption of BA synthesis has a negative impact on intestinal health, putatively increasing intestinal damage and gut permeability, with the potential to drive pathogenesis of NAFLD.

DOI: 10.1530/endoabs.65.OP3.2

OP3.3

The impact of subcutaneous infusions of three anorexigenic gut hormones glucagon-like peptide-1, oxyntomodulin and peptide YY (GOP) on the psychological health of obese diabetic patients

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Introduction
Obesity-associated psychopathological co-morbidities have a negative impact on quality of life. Roux-en-Y gastric bypass surgery (RYGB) has been shown to ameliorate psychological health, however, the underlying mechanisms are not fully understood. Changes in gastrointestinal and central neuroendocrine signalling have been postulated as mediators of psychological and eating behaviour changes following RYGB. Here we assess the impact of subcutaneous infusions of three anorexigenic gut hormones glucagon-like peptide-1, oxyntomodulin and peptideYY (GOP) on the psychological health of obese diabetic patients.
Method
In this prospective cohort study, 27 obese diabetic patients were recruited and randomized to GOP ($n=16$) or saline ($n=11$) infusion for 4 weeks. We also studied 16 patients who underwent RYGB. A set of validated questionnaires were used to measure psychological health, eating psychopathology, and quality of life pre- and post-intervention. Results were analysed using two-way ANOVA followed by *post-hoc* analysis using the Bonferroni method to correct for multiple corrections.
Results
Both GOP and RYGB showed an improvement of health-related quality of life related to weight loss. There was a significant increase in restrained eating and a significant reduction in external eating in the GOP group, an improvement on reward and punishment sensitivity assessed by the Behavioural Inhibition System and Behavioural Activation System (BIS/BAS) scales after GOP compared with the saline group. There was a significant improvement in the RYGB group the Power of Food Scale, a questionnaire that measures an individual's motivation to consume highly palatable foods. These results emphasise the effectiveness of the surgical intervention in ameliorating obesity-related symptoms whilst providing substantial long-lasting weight-loss effects.
Conclusion
The improvement in the reward sensitivity post-GOP warrants further research using longer-term studies. The augmented secretion of anorexigenic hormones post RYGB in its own may not be the only mediator for the favourable improvement in psychological health seen after RYGB.

DOI: 10.1530/endoabs.65.OP3.3

OP3.4

Mice with a gain-of function Gα_{11} mutation have autosomal dominant hypocalcaemia, but not impaired glucose metabolism

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The calcium-sensing-receptor (CaSR) is a G-protein-coupled receptor that plays a fundamental role in extracellular calcium homeostasis, but is also implicated in non-calcitropic disorders including colon cancer and asthma. In addition, CaSR is highly expressed in pancreatic islets where it has a role in insulin secretion. Patients with gain-of-function CaSR mutations, and mice (referred to as Nuf) with a gain-of-function CaSR mutation (Leu723Gln), develop autosomal dominant hypocalcaemia type-1. Nuf mice also have impaired glucose tolerance, reduced insulin secretion, and decreased pancreatic islet size and proliferation, indicating a role for CaSR in pancreatic islets. Patients with gain-of-function mutations of the Gα_{11} protein, which mediates CaSR signalling, and mice (referred to as Dsk7) with a gain-of-function Gα_{11} mutation (Ile62Val), develop ADH2. We therefore investigated Dsk7 mice for defects in glucose metabolism and islet architecture. Wild-type ($n=21$), heterozygous ($n=24$) and homozygous ($n=9$) Dsk7 mice were aged for 14 weeks and intraperitoneal glucose tolerance tests were performed. Heterozygous and homozygous Dsk7 mice, compared to wild-type, were confirmed to have hypocalcaemia (plasma adjusted-calcium of 2.06 ± 0.08 and 1.72 ± 0.08 mmol/l, and 2.37 ± 0.09 mmol/l respectively, $P<0.0001$), consistent with ADH2. However, significant differences in glucose tolerance were not observed. Pancreatic islet size and number, assessed by haematoxylin and eosin staining of paraffin-embedded tissue sections, did not differ between wild-type ($n=10$), heterozygous ($n=8$) and homozygous ($n=9$) Dsk7 mice. Islet architecture was further studied by immunofluorescence microscopy using antibodies against insulin, glucagon and the proliferation marker Ki-67. Image analyses of >144 islets per genotype ($n=8$ mice) revealed no difference in α- and β-cell number and proliferation. In conclusion, our findings indicate that Gα_{11} gain-of-function does not influence glucose homeostasis or pancreatic islet architecture. Thus, the glucose phenotype observed in the Nuf mice is likely transduced by G-proteins other than G$\alpha_{11,}$ or is due to G-protein independent mechanisms.

DOI: 10.1530/endoabs.65.OP3.4

Bone and Calcium

OP4.1

Oral calcium loading test can predict the progression of hypercalcaemic primary hyperparathyroidism in patients with normocalcaemic hyperparathyroidism

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Introduction
Normocalcaemic hyperparathyroidism (nHPT) is a persistently elevated parathyroid hormone (PTH) with normal ionised calcium levels in the absence of secondary hyperparathyroidism. nHPT is proposed to be an earlier phase of hypercalcaemic primary hyperparathyroidism (PHPT). nHPT patients can present with progressive complications such as osteoporosis and nephrolithiasis. Currently, there is no diagnostic test to confirm primary hyperparathyroidism in nHPT patients, leading to a delay in curative parathyroidectomy. The aims of this study were to determine:
1) if the oral calcium-loading test (OCLT) can predict the progression of nHPT to PHPT
2) if the OCLT results are better predictors of PHPT progression than baseline calcium and PTH.

Methods
A retrospective data analysis of nHPT patients who underwent the OCLT between August 2016 and January 2019. Adjusted-calcium and PTH levels were evaluated at 0, 60, 120 and 180 min after calcium ingestion. Two-hours urine calcium: creatinine ratio was measured at baseline and 120–240 min post-calcium ingestion. On analysis, patients were classified as; 12 PHPT; having progressed to PHPT, 8 nHPT and 8 normal.
Results
Baseline calcium was significantly higher in the PHPT compared to the nHPT group, with a large overlap between the groups. Nadir PTH, 3-h PTH, and Product-P (nadir PTH x peak calcium concentration) were significantly higher while percentage PTH decrease was significantly lower in the PHPT group compared to the nHPT and normal groups ($P<0.01$). No statistical differences were found between the PHPT and nHPT groups in other parameters.
Conclusion
The OCLT can predict PHPT progression in nHPT patients, with; nadir PTH, Product-P, 3-h PTH, and percentage PTH decrease. These are better predictors than baseline calcium and PTH. Prospective studies are needed to establish the diagnostic threshold for primary hyperparathyroidism in nHPT patients. The implication being that these patients could be offered early surgery to reduce the risk of complications.

DOI: 10.1530/endoabs.65.OP4.1

OP4.2

Identification of novel pathogenic variants and phenotypic features in patients with pseudohypoparathyroidism and acrodysostosis, subtypes of the newly defined inactivating PTH/PTHrP signalling disorders (iPPSD) classification system

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Due to overlapping clinical and biochemical features, disorders now known to be molecular defects in the parathyroid hormone (PTH)-receptor signalling pathway, such as Albright Hereditary Osteodystrophy (AHO), pseudohypoparathyroidism (PHP), and acrodysostosis, have been historically confused. AHO is a complex disorder defined by the presence of a short adult stature relative to the height of an unaffected parent and brachydactyly type E, as well as a stocky build, round face, and ectopic calcifications. PHP describes end-organ resistance to PTH, occurring with or without the physical features of AHO. PTH resistance was initially considered an obligatory manifestation of AHO, with the terms AHO and PHP used interchangeably. However, it was later recognised that AHO can occur in the absence of PTH resistance, termed pseudopseudohypoparathyroidism (PPHP). PHP and PPHP are aetiologically linked and caused by genetic and/or epigenetic alterations in the guanine nucleotide-binding protein alpha-stimulating (Gsα) locus (GNAS) in chromosome 20q13. Acrodysostosis, a less-recognised group of skeletal dysplasias, partially overlap with skeletal, endocrine, and neurodevelopmental features of AHO/PHP, and can be overlooked in clinical practice, causing confusion in the literature. Acrodysostosis is caused by defects in two genes, PRKAR1A and PDE4D, both encoding important components of the Gsα-cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA) signalling pathway. Here we describe the clinical course and genotype of two adult patients with overlapping AHO features who harboured novel pathogenic variants in GNAS (c.2273C>G, p.Pro758Arg, NM_080425.2) and PRKAR1A (c.803C>T, p.Ala268Val, NM_002734.4), respectively. The cases of these two patients highlight the value of expert radiological opinion and molecular testing in establishing correct diagnoses, and we discuss phenotypic features of our patients, including the first description of subcutaneous ossification and spina bifida occulta in PRKAR1A-related acrodysostosis, in the context of the novel inactivating PTH/PTH related peptide (PTHrP) signalling disorder (iPPSD) classification system.

DOI: 10.1530/endoabs.65.OP4.2

OP4.3

Mendelian randomization and machine learning to assess the causal association of Type 2 Diabetes with osteoporosis and fragility fractures

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Background
We used Mendelian randomization and machine learning (gradient boosting) to assess the causal association of Type 2 Diabetes with osteoporosis.
Methods
We selected 155 SNPs associated with type 2 diabetes and glycaemic and insulin-related traits reported in previous studies (1,2) and studied the association with Heel bone mineral density (BMD)) ($n=$ 4 72 996) and risk of fragility fractures (26 157 cases and 17 807 controls) in UKBiobank participants. The association of the SNPs was tested with BMD using a linear regression model with adjustment for top 5 principal components, age, sex, smoking and BMI. The association of the top SNPs ($P<$10-8) was also tested in a subset sample of 26 157 cases with fragility fractures and 17 807 controls using a logistic regression model with covariate adjustments. In the gradient boosting analysis those with BMD less than the first quartile of distribution was categorised as low BMD while those above it as high BMD and age, sex, smoking and BMI and 155 SNPs were included as predictor variables. All the statistical analysis was done in R3.5.5.
Results
The study consisted of 4 72 996 participants in UKBiobank 52% female with median BMD of 0.52 (IQR 0.44–0.60). Of the 155 SNPs associated with T2D and glycaemic traits, 17 SNPs from 11 gene/loci were associated with BMD at genome-wide significance ($P<$1-08). The top associated SNPs with BMD included rs2745353 in *RSPO3*, rs983309 in *RP11*, rs6072275 in *RP1* rs174576 in *FADS2*, rs10203174 in *THADA* and rs1727313 in *MPHOSPH9*. SNPs in *RSPO3* and *RP11* were associated with the risk of fragility fractures. The gradient boosting analysis confirmed the results of the regression analysis.
Conclusion
We used Mendelian randomization and machine learning to show that type 2 diabetes is causally associated with BMD and risk of fragility fractures.

DOI: 10.1530/endoabs.65.OP4.3

OP4.4

The associations between body fat distribution and bone mineral density in the Oxford Biobank: a cross sectional study

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Aims
Body composition is associated with bone mineral density, but the precise associations between body fat distribution and bone mineral density (BMD) remain unclear. We hypothesised that the regional adipose tissue depots would have independent associations with BMD.
Methods
We used data from 4900 healthy individuals aged 30–50 years old from the Oxford Biobank to analyse associations between regional fat mass and lean mass with total BMD.
Results
Lean mass was strongly positively associated with BMD. After adjustment for relevant confounders, total body fat was significantly positively associated with BMD in lean, but not obese, men and women. An overall positive association was observed between total BMD and all fat depots measured either by anthropometry or DXA when accounted for lean mass. However, on mutual adjustment with both total fat and lean mass, both android fat ($s\beta=-0.360$, $P=7.80\times10^{-05}$) and visceral adipose tissue (VAT; $s\beta=-0.144$, $P=2.41\times10^{-04}$) showed directionally opposite effect; a significant decrease in total BMD was observed with increasing android fat and VAT in men while in women only VAT was significantly associated with lower BMD ($s\beta=-0.151$, $P=1.72\times10^{-07}$). Directionally similar association was also observed with waist circumference in men ($P=0.001$). Most of these associations, except for VAT in women, were not significant when adjusted for HOMAIR.
Conclusions
These results show that the distribution of fat alters the association between adiposity and BMD, possibly mediated by its effect on insulin resistance.

DOI: 10.1530/endoabs.65.OP4.4

Reproductive Endocrinology and Biology

OP5.1

Hypothalamic-pituitary-gonadal (HPG) axis suppression during basic military training in women despite increased adiposity and insulin resistance

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Background
Low energy availability (LEA) in female athletes can result in HPG axis suppression. Basic military training (BMT) is physically arduous and associated with amenorrhoea and low-trauma fractures. We hypothesised that women undergoing BMT would demonstrate evidence of LEA and suppressed HPG function.
Design
Prospective study of 61 women undertaking 11-month BMT. Subjects acted as their own controls at baseline (all measures). Body composition measurement (DXA) was repeated after 3, 7 and 11 months; fasting blood (glucose, insulin (for homeostatic model of insulin resistance, HOMA2), leptin, inhibin B, estradiol,

anti-Müllerian hormone (AMH), and FSH) after 7 and 11 months, and dynamic 1-h 10 μg GnRH test measuring LH and FSH after 7 months. Menstruation and ovulation were assessed in non-contraceptive pill-users ($n=22$) using diaries and weekly urinary progesterone : creatinine ratio, respectively.

	Baseline	7 months	11 months
HOMA2	1.77 ± 0.52	1.85 ± 0.30*	2.06 ± 0.61*
Leptin, ng.ml^{-1}	8.09 ± 3.11	11.37 ± 4.10*	12.52 ± 4.12*
Inhibin B, pg.ml^{-1}	26.8 ± 10.9	54.0 ± 30.8*	42.3 ± 27.6*
Estradiol, pmol.l^{-1}	83 ± 46	145 ± 73*	95 ± 64
AMH, pmol.l^{-1}	24.1 ± 18.6	22.5 ± 14.3	22.4 ± 14.8

Results

52 women, aged 24.0 ± 0.3 years, completed the study. Fat mass decreased 0.8 kg from baseline to month 3, increased 1.8 kg to month 7 and reverted to baseline by month 11 ($P<0.001$). Fat-free mass did not change ($P=0.13$). HOMA2 and leptin increased (both $P<0.001$), as did estradiol and inhibin B ($P<0.05$) while AMH was unchanged ($P=0.6$) (Table). Maximum and area-under-the-curve fold-responses of LH and FSH to GnRH were suppressed after 7 months (both $P<0.001$). Findings were unaffected by contraceptive use (effect × time $P=0.8$). Seven participants (32%) became oligo/amenorrhoeic. 87% of regular (23–35d) cycles were anovulatory.

Conclusion

Evidence of adiposity-related adaptation suggests non-LEA stressors contributed to HPG axis suppression and follicular dysgenesis. Further studies are required to deliniate causes of reproductive dysfunction and associated pathology in military women.

DOI: 10.1530/endoabs.65.OP5.1

OP5.2

Profiling the expression and function of the truncated oestrogen receptor isoform ER46 in human endometrium

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Introduction

Oestrogen receptors (ER) are essential for reproductive function and fertility. ER46 is a 46 kDa truncated isoform of full length ERα (ER66) that binds oestradiol (E2) and can signal via nuclear or membrane-initiated signalling pathways. ER46 has been detected in breast cancer cell lines but expression in endometrial tissues has not been documented. The aims of this study were a) to determine whether endometrial cells express ER46, and b) to investigate a potential functional role for ER46 in regulating oestrogen responses in the endometrium.

Methods

Primary human endometrial ($n=20$) and first trimester decidual tissue biopsies ($n=18$) were collected using methods approved by the local institutional ethics committee (LREC/05/51104/12 and LREC/10/51402/59). Uterine Natural Killer (uNK) cells were freshly isolated from decidua ($n=8$) by magnetic bead sorting. The expression of oestrogen receptors (ER66, ER46 and ERβ) was assessed by qPCR, western blot and immunohistochemistry. Cell motility was measured in uNK cells by live cell imaging; cells were treated with E2-BSA (10 nM equivalent), the ERβ-selective agonist DPN (10 nM) or vehicle control (DMSO).

Results

ER46 was detected by qPCR and western blot in endometrial tissues and was the predominant ERα isoform in first trimester decidua ($P<0.01$). Immunohistochemistry identified putative ER46 immunolocalised to the nuclei, cytoplasm and cell membrane of endometrial cells. Analysis of decidual tissues demonstrated that uNK cells, a specialised leukocyte population which is abundant in early pregnancy, were uniquely ER66^{neg}/ER46^{pos} with ER46 localised to the cell membrane. ER46 expression was confirmed in isolated uNK cells where selective activation of ER46 with E2-BSA significantly increased cell velocity ($P<0.001$) and distance ($P<0.001$) compared to DPN or vehicle control.

Conclusions

These novel findings identify a role for ER46 in regulating oestrogen responsiveness of the endometrium and provide unique insight into the regulation of uNK cell activity during the establishment of pregnancy in women.

DOI: 10.1530/endoabs.65.OP5.2

OP5.3

Stress is implicated in programming metabolic disorders in the offspring of fructose-induced diabetic rats

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Foetal exposure to a diabetic intra-uterine environment is known to impair metabolic processes with long term consequences, a phenomenon termed foetal programming. However, the mechanisms involved has not been completely understood. Fructose feeding has been used to induce type 2 diabetes in animal models. This study aims to investigate if stress mechanism is involved in the foetal programming of diabetic pregnancies. Twenty-four female rats were randomly divided into two groups namely group A (control): rats fed with normal rat chow and group B (Fructose-induced diabetes): rats made diabetic using a diet consisting of 25% fructose. Diabetes was confirmed after 8 weeks of fructose feeding. Rats in both groups were mated, pregnancy was confirmed and rats sub-grouped into 2 namely day 19 of pregnancy and term rats. Maternal blood and amniotic fluid samples were obtained from day 19 group and assessed for glucose, insulin, corticotrophin releasing hormone (CRH) and corticosterone levels. Term rats were allowed to deliver; the offspring were weaned and fed with normal rat chow till the onset of puberty. Offspring blood samples were obtained and assessed for glucose, insulin, corticosterone, lipids and liver enzyme levels. Oral glucose and insulin tolerance tests were also conducted. Results showed that maternal and amniotic fluid glucose, insulin, CRH and corticosterone levels were significantly increased in the diabetic rats ($P<0.05$). The offspring of diabetic rats had a significantly increased birth weight, glucose, insulin, corticosterone and lipid levels ($P<0.05$) with no significant difference in liver enzyme levels. Glucose and insulin tolerance test results were deranged, while positive correlations exist between maternal and offspring glucose, insulin, and corticosterone levels in the diabetic rats. These findings show that maternal diabetes triggers stress mechanism in both maternal and foetal circulations, leading to impaired glucose and lipid metabolism in the offspring.

DOI: 10.1530/endoabs.65.OP5.3

OP5.4

Kisspeptin as a novel biomarker for pregnancy complications

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Background

Placentation (invasion of the placenta into the maternal endometrium) is hypothesised to be critical for healthy placental function and is abnormal in two thirds of miscarriages. Kisspeptin has emerged as a putative regulator of physiological placentation; it is highly expressed in placental syncytiotrophoblasts and could play an important paracrine role in the regulation of placentation. Circulating kisspeptin levels are considerably raised during healthy pregnancy and reduced in women with miscarriage. We aimed to investigate the utility of circulating kisspeptin concentrations in the assessment of pregnancy complications.

Methods

This study was performed in collaboration with the Early Pregnancy Outcome Study (EPOS), which aims to identify novel pregnancy biomarkers. Women were invited to attend for blood-sampling, clinical and ultrasound assessment fortnightly during the first trimester and again during the second and third trimesters. Asymptomatic women with healthy pregnancy ($n=265$) provided 960 blood-samples. Women with pregnancy complications including miscarriage ($n=95$), pre-eclampsia (PET; $n=24$), pregnancy induced hypertension (PIH; $n=14$), gestational diabetes (GDM; $n=41$), preterm birth (PTB; $n=14$) and intrauterine growth restriction (IUGR; $n=24$) provided 569 blood-samples.

Results

Gestation-adjusted circulating kisspeptin and βhCG levels were 66% and 57% lower, respectively, in women with miscarriage compared to healthy pregnant controls ($P<0.0001$). Area under ROC curve for diagnosis of miscarriage was greater for the combination of both kisspeptin and βhCG together (0.92) than for either measure alone (βhCG 0.859, kisspeptin 0.874). An adjusted logistic regression model revealed that an 100 pmol/l increase in plasma kisspeptin

reduced the odds of miscarriage by 42%. Gestation-adjusted kisspeptin levels were lower in women with GDM ($P=0.002$), or IUGR ($P<0.0001$), and higher in women with PTB ($P=0.004$). Kisspeptin increased with gestation greater in PET ($P=0.008$) and PIH ($P<0.0001$) than in healthy controls.
Conclusions
Plasma kisspeptin is a promising biomarker for pregnancy complications and provides additional diagnostic capability over that provided by βhCG.
DOI: 10.1530/endoabs.65.OP5.4

Neuroendocrinology, Pituitary and Neoplasia

OP6.1

Extended TSS (guided by 11C-methionine PET + MRI (Met-PET/MRCR)) can be an effective treatment option for patients with persistent acromegaly due to previously deemed unresectable lateral disease

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Objective
To determine if an extended lateral approach to trans-sphenoidal surgery (TSS), guided by ^{11}C-Methionine PET/CT co-registered with volumetric MRI (Met-PET/MR^{CR}), can lead to remission in patients with persistent acromegaly due to post-operative lateral/para-sellar tumour remnants.
Methods
We identified eight patients with persistent acromegaly following primary intervention [TSS ± medical therapy ± radiotherapy (RT)], in whom further surgery had initially been discounted due to suspected unresectable lateral/para-sellar disease. All patients underwent Met-PET/MRI^{CR}. Scan findings were used by the pituitary multidisciplinary team to inform decision-making with regards to repeat surgery. Extended TSS was performed with wide lateral exploration as guided by the findings of Met-PET/MRI^{CR}.
Results
Met-PET/MRI^{CR} demonstrated lateral/parasellar tracer uptake in areas of suspected residual disease in all studied patients. Physiological uptake was also seen within the normal pituitary gland. At surgery, in five patients tumour was identified and resected, although histology confirmed somatotroph tumour in only four cases. In the other three patients, no definite tumour was seen, but scar tissue was removed. However, despite the uncertainty at surgery, all patients achieved significant post-operative clinical and biochemical improvement [Insulin like growth factor (IGF-1) < 1.2 (the upper limit of normal (ULN) in all cases, and fully normalised in six patients], Figure 1. These findings were maintained for up to 28 months (mean follow up in all patients = 13 months). No patient suffered any additional pituitary deficit or other complication of surgery.
Conclusion
PET-guided extended surgery may be an effective treatment in patients with persistent acromegaly due to lateral/parasellar disease.
DOI: 10.1530/endoabs.65.OP6.1

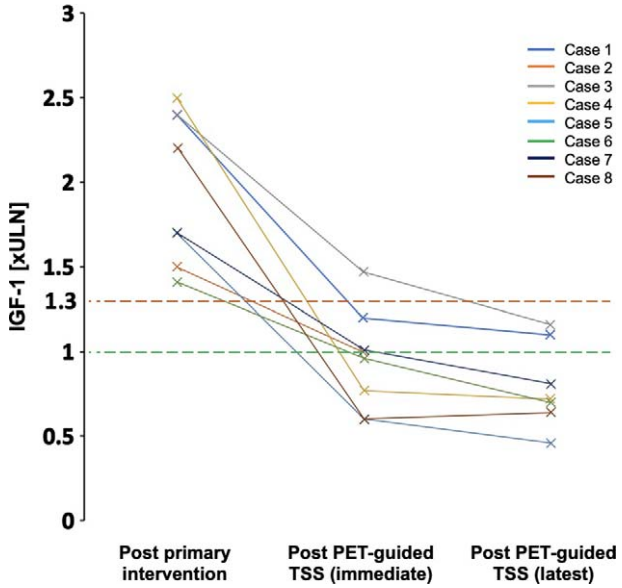

Figure 1 IGF-1 levels (expressed in relation to the ULN (upper limit of normal)) measured at three time-points. The 'immediate' post-PET-guided TSS timepoint was performed at 6-weeks whereas the latest measurement was performed at varying intervals, averaging at 13 months post-PET-guided TSS.

OP6.2

Transcriptomic analyses reveal deregulation of focal adhesion pathway in *Aip* KO mice and AIP mutation positive human tumours

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Introduction
AIP mutations are responsible for 15-30% of cases of familial isolated pituitary adenomas. The pathophysiology that drives this AIP-related pituitary tumorigenesis is not fully understood. We developed a pituitary-specific *Aip* knockout (KO) mouse model, which mostly recapitulates the human phenotype.
Aims
To performed comparative gene expression analysis of *Aip*-KO mouse pituitary tumours and AIP mutation positive human pituitary tumours in order to identify the genes and signalling pathways involved in Aip-related pituitary adenoma progression.
Methods
RT-qPCR was performed to confirm the expression of the selected candidate genes at the mRNA level. Immunofluorescence immunohistochemistry on mouse pituitary sections and immunoblotting for *Aip*-KO embryonic fibroblast were used to validate the changes at the protein level.
Results
Comparative gene expression analysis of *Aip*-KO mouse RNA-seq and human *AIP* mutation positive microarray gene expression data identified 50 common genes. 11 of 50 genes were statistically significantly differentially expressed with the same direction of change. Pathway analysis of these genes revealed that FAK pathway is one of the significant altered pathways. Five genes (*Actg1, Col6a1, Itgb6*, *Lamc2* and *Cdh3*) from this pathway were selected for further validation. As well as a separate gene (*Cdc42*) that had been implicated in our human data and rat cell-line. Our data suggests that the development of Aip-related pituitary adenomas may be mediated by the altered expression of these genes. We validated these data at the protein level with immunofluorescence using *Aip*-KO embryonic fibroblast and immunofluorescence immunohistochemistry in pituitary-specific *Aip*-KO pituitary. ITGB6 and LAMC2 were downregulated in the *Aip*-KO fibroblasts and mouse model.
Conclusion
ITGB6 and LAMC2 are important proteins for focal adhesion, the down-regulation of ITGB6 and LAMC2 may lead to dysfunction of this pathway, which may lead to the pituitary tumorigenesis associated with *AIP* deficiency.
DOI: 10.1530/endoabs.65.OP6.2

OP6.3

JQ1 treatment significantly reduces POMC expression and ACTH secretion from the corticotrophinoma cell line, AtT20

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Corticotrophinomas represent >10% of all surgically removed pituitary adenomas, which are the most commonly encountered intracranial neoplasms that are identified in >25% of unselected autopsies and approximately 20% of the population undergoing intracranial imaging. Corticotrophinomas are associated with hypersecretion of adrenocorticotropic hormone (ACTH), which leads to excessive production of glucocorticoids by the adrenal cortex and the resulting hypercortisolemia causes Cushing's syndrome. Medical treatments for corticotrophinomas are limited, and we have previously reported that (+)-JQ1 (JQ1), an epigenetic inhibitor of the bromo and extra-terminal (BET) protein family, which bind acetylated histones to regulate gene transcription, significantly reduced cell proliferation, and increased apoptosis of the murine ACTH-secreting corticotrophinoma cell line AtT20. Here, we report the results of RNA Sequencing analysis, which reveals that JQ1 treatment could also down regulate expression of the pro-opiomelanocortin (*Pomc*) gene that encodes the precursor protein of ACTH. Using quantitative reverse transcription PCR, we confirmed the down regulation of *Pomc* (16.7-fold, $P<0.005$), in JQ1 treated, compared to control compound (JQ1-) treated cells. Western blot analysis also confirmed that POMC protein expression was decreased after JQ1 treatment, with significant reductions observed after 24 h (4.4-fold, $P<0.0005$), 48h (6.3-fold, $P<0.0005$) and 72 h (5.1-fold, $P<0.005$), compared to control JQ1- treated cells. To determine if the reduction in POMC expression also resulted in a reduction of ACTH secretion we performed an enzyme linked immunosorbant assay (ELISA) on AtT20 cell media collected up to 72 h after JQ1 treatment. We found that the levels of ACTH in cell media were significantly decreased at 48 h (1.4-fold, $P<0.0005$) and 72 h (1.2-fold, $P<0.05$) after JQ1 treatment, when compared to JQ1- treatment. Thus, our data indicate that JQ1 can significantly decrease ACTH secretion, through reduction of POMC expression, and therefore JQ1 may provide a novel approach for the control of hormone secretion in corticotrophinomas.

DOI: 10.1530/endoabs.65.OP6.3

OP6.4

Urine steroid metabolomics as a novel diagnostic tool for recurrent adrenocortical carcinoma detection

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Objective
Urine steroid metabolomics, combining mass spectrometry-based steroid profiling and machine learning, has been described as a novel diagnostic tool for detection of adrenocortical carcinoma (ACC). This proof-of-concept study evaluated the performance of urine steroid metabolomics as a tool for post-operative recurrence detection after microscopically complete (R0) resection of ACC.
Methods
135 ACC patients from 14 clinical centres provided post-operative urine samples, which were analysed by gas chromatography-mass spectrometry. We assessed the utility of these urine steroid profiles in detecting ACC recurrence, either when interpreted by three expert clinicians, or when analysed by Random Forest, a machine learning-based classifier. Radiological recurrence detection served as the reference standard.
Results
Imaging detected recurrences in 32 patients who provided pre- and post-recurrence urines, while 39 of 135 patients remained disease-free for >3 years. The urine 'steroid fingerprint' at recurrence resembled that observed in the urine before R0 resection of ACC in the majority of cases. Expert review of longitudinally collected urine steroid profiles detected recurrence by the time of radiological diagnosis in 50–72% of cases, improving to 69–92%, if a urine steroid result pre-excision of the primary tumour was available. Mitotane use did not affect diagnostic success. Recurrence detection by steroid profiling preceded diagnosis by imaging by more than 2 months in 22–39% of successful detections. Specificities varied considerably between the experts (61%–97%). The computational classifier detected ACC recurrence with superior accuracy (sensitivity = specificity = 81%). The deoxycortisol metabolite tetrahydro-11-deoxycortisol (THS) was the single most important steroid metabolite in differentiating post-recurrence urine samples from samples provided by non-recurred patients, followed by the mineralocorticoid precursor metabolite tetrahydrocorticosterone (THDOC) and the pregnenolone metabolite pregnenediol (5-PD).
Conclusion
Urine steroid metabolomics is a promising non-invasive, radiation-free tool for post-operative recurrence detection in ACC; availability of a pre-operative urine considerably improves the ability to detect ACC recurrence.

DOI: 10.1530/endoabs.65.OP6.4

Featured Clinical Case Posters

CC1

Double somatic mutations of CTNNB1 and GNA11 in aldosterone producing adenomas (APAs) presenting in puberty, pregnancy or menopause

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Objective
We reported 3 patients with primary aldosteronism who presented at times of high plasma LH, and had somatic CTNNB1 mutations causing ~100-fold elevation of LHCGR in their APAs (Teo *et al*. NEJM 2015). Subsequently we identified 4 further patients, but the association with pregnancy was not found by others. Whole exome sequencing (WES) of an APA diagnosed at onset of puberty suggests an explanation.
Method
WES of tumour and blood was performed in a 12-year old boy with severe hypertension. Candidate genes were Sanger sequenced in 6 other APAs with known or suspected CTNNB1 mutations. LHCGR expression was measured in all 7 APAs by qPCR. Function of mutant genes was assessed by measurement of aldosterone production by NCI-H295R adrenocortical cells and primary human APA cells.
Results
The boy's APA had S45F mutation of CTNNB1 and Q209P mutation of GNA11. Mutations of Q209, to P or H, were found in all 6 patients with previously identified mutations of CTNNB1 (S33C, S45P, T41A, G34R, or S45F). qPCR showed 32–166 fold increase in expression of LHCGR in the APAs compared with the normal adjacent adrenal tissue. H295R cells (whose CTNNB1 genotype is S45P) were GNA11 wild-type. In cells transfected with CTNNB1 wild-type, aldosterone secretion fell by 51% ($n=3$, $P<0.001$). Q209P transfection increased aldosterone by 277% ($n=3$, $P<0.05$). Primary human APA cells electroporated with both GNA11 Q209H and CTNNB1 del45 group showed a twfold increase in aldosterone secretion compared to single-mutant transfected cells ($n=3$, $P<0.01$).
Conclusions
Double somatic mutations of CTNNB1 and GNA11 may be required to induce reversion to gonadal phenotype, causing LHCGR-expressing APAs to present at times of high LH. GNA11 mediates the aldosterone response to AngII, and Q209 mutations cause uveal melanomas. They are in the analogous residue to Q227 mutations of GNAS which activate cAMP in McCune Albright.

DOI: 10.1530/endoabs.65.CC1

CC2

Splice-site mutations in the melanocortin-2 receptor accessory protein that lead to early-onset familial glucocorticoid deficiency type 2

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Background
Familial glucocorticoid deficiency (FGD) is characterised by isolated glucocorticoid deficiency, with preserved mineralocorticoid production. FGD type 2 is caused by mutations in *MRAP* encoding the melanocortin-2 receptor accessory protein. MRAP has a single transmembrane domain essential to its function in trafficking the MC2R/ACTH receptor. 15 mutations in *MRAP* have been described, five of which are within the canonical donor splice-site of intron 3 and predicted to cause complete exon skipping.
Patients and methods
Proband 1 (family 1) was diagnosed at 13 months. His sibling was hyperpigmented but was neither formally diagnosed nor treated and died neonatally after a febrile illness. Proband 2 (family 2), diagnosed at birth, was hyperpigmented with elevated ACTH levels. Both patients have responded to hydrocortisone replacement therapy. The coding exons of *MC2R* and *MRAP* were Sanger sequenced from patient DNA. The effect of splice-site mutations was assessed *in silico* by Human Splicing Finder (HSF3.0) and *in vitro* by a splicing assay, comparing wild type and mutant heterologous minigenes.
Results
Homozygous mutations, c.106+1delG (family 1) and c.106+2dupT (family 2) were identified in the donor splice-site of intron 3 of *MRAP*. HSF3.0 predicted c.106+1delG destroys the splice site and c.106+2dupT weakens it. However, there is another high-scoring donor site 23 bp downstream which, if utilised, would result in the addition of frame-shifting 22 bp for c.106+1delG BUT the possibility of in-frame insertion of 24 bp for the c.106+2dupT mutation. An *in vitro* splicing assay utilised to assess this demonstrated that both variants resulted in complete skipping of exon 3.
Conclusion
Both splice-site mutations lead to complete skipping of exon 3 of *MRAP*, containing the translational start site, the next methionine from which translation could start is after the essential transmembrane domain. Hence, this is likely to result in the absence of any functional protein which is in keeping with the severe, early presentation in these two families.

DOI: 10.1530/endoabs.65.CC2

CC3

A rare sclerosing bone dysplasia

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A 30 year old woman presented with two year history of right lower leg pain. The pain was constant, worse in cold weather, not worsened by weight bearing and occasionally woke her from sleep. On examination she was tender on palpation of mid distal right tibia. X ray showed sclerotic portions of right tibia and fibula. MR lower right leg demonstrated extensive area of intramedullary bone marrow oedema in the distal half of the right tibia with associated cortical thickening and periosteal reaction. NM Bone scan had increased uptake in midshaft of the right tibia, distal shafts of both femora and ulnar shafts. MR forearms and femurs revealed no obvious bone expansion with predominant inwards growth, and in the left forearm almost complete obliteration of the fat in the medullary bone. Adjusted calcium, Alkaline phosphatase, phosphate and vitamin D were normal. Genetics confirmed diagnosis of Camurati Engelmann disease, a rare sclerosing bone autosomal dominant dysplasia due to a mutation of the Transforming growth factor β-1(TGFβ1) gene. Affected individuals present with bone pain commonly of the legs, muscle weakness and easy fatigability between 20 and 50 years old. Clinical examination usually reveals bony tenderness on palpation. The patient may often be slender or marfanoid. Radiologically the most common finding is cortical thickening of the diaphysis of the long bones. Hyperostosis may be bilateral or asymmetric. The skull is also commonly involved with sclerosis of the skull base. Bone mineral density is usually increased therefore bone scintigraphy has been suggested to be helpful to aid in monitoring. Treatment strategies such as losartan, thought to downregulate TGFβ1 signalling, and steroid use have been suggested in the literature to reduce pain. The patient is currently being trialled on losartan therapy. Due to the rarity of this disease the exact protocol for follow up is unclear.

DOI: 10.1530/endoabs.65.CC3

CC4

Multiple endocrine neoplasia type 1 (MEN1) mosaicism caused by a c.124G>A variant in the MEN1 gene

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The MEN1 gene is positioned on the long arm of chromosome 11 (11q13) and results in production of the protein menin. MEN1 mutations produce aberrant menin action or production, although the relationship with tumourigenesis is not clear. Mosaicism is extremely rare, a recent report citing two mosaic cases reported by next generation sequencing[1]. We describe a 43 year old woman with MEN1 mosaicism associated with parathyroid adenoma and probable pancreatic gastrinoma. Our patient initially presented in 2017 with nephrolithiasis alongside

biochemistry that confirmed primary hyperparathyroidism (adjusted Calcium 2.96 mmol/l (2.2–2.6 mmol/l) and PTH 15.9 pmol/l (1.6–7.5 pmol/l)) and imaging confirming a right lower pole parathyroid adenoma. Whilst awaiting her parathyroidectomy, in June 2018 she was admitted with a perforated duodenal ulcer within the first part of the duodenum, ascribed to analgesic ibuprofen. She remained hypercalcaemic post adenoma removal and imaging (later confirmed on pathology) denoted a further culprit right paratracheal parathyroid adenoma which was subsequently removed in March 2019. Whilst her calcium remains normal, a second duodenal perforation (D2) requiring surgery prompted consideration of MEN1. DNA was extracted for next generation sequencing which revealed mosaicism with a c.124 G>A variant in the MEN1 gene at a level of approximately 15%. This variant predicts an amino acid substitution p.(Gly42Ser) in menin structure - an amino acid change previously associated with MEN1[2]. This lady has no first degree family history of note and is hence an index case. Gut hormones and pituitary MRI are awaited. Given the paucity of MEN1 mosaicism reported within the literature, any possible putative hypothesis about a more benign natural history, given the presence of the two cell lines and only 15% mosaicism, is tempting but not possible.

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DOI: 10.1530/endoabs.65.CC4

CC5

Pituitary carcinoma with hepatic metastasis hypersecreting ACTH precursors masquerading as Nelson syndrome after bilateral adrenalectomy for refractory Cushing's syndrome

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Pituitary carcinomas are extremely rare accounting for only 0.1%–0.2% of all pituitary tumours. The diagnosis is primarily dependent on aggressive imaging characteristics and high tumour mitotic activity on histology. A 47 year old gentleman with Type 1 Diabetes presented with an apparent non-functioning pituitary macro adenoma which was resected transsphenoidally and followed by EBRT. Initial histology was negative for ACTH. He presented 2 years later with florid Cushing's syndrome. Bilateral adrenalectomy was performed in view of the absence of a definitive pituitary surgical target. The patient subsequently presented with marked weight loss and progressive generalised hyperpigmentation suggestive of Nelson's syndrome. ACTH levels were moderately elevated at 67 ng/l. Cranial imaging excluded a recurrence of pituitary tumour. Whole body CT revealed a large hepatic lesion with portocaval lymphadenopathy. ACTH precursor levels were markedly elevated at 159 750 (Normal range <40). The liver lesion was surgically resected and histopathology was positive for synaptophysin and ACTH with features indicative of a neuroendocrine tumour. Ki67 proliferation index was 21%. Retrospective review of initial pituitary histology showed positive staining for ACTH and Ki67 index of 13% suggesting metastatic pituitary carcinoma.

Conclusion

Pituitary carcinomas are extremely rare accounting for 0.1%–0.2% of all pituitary tumours. Invasive Pituitary adenomas with a Ki67 proliferation index >3% should be followed up closely. Diagnostic molecular markers and cancer immunotherapy drugs offer additional treatment options in cases where re-do pituitary surgery or stereotactic radiotherapy are contraindicated. A high index of suspicion remains the cornerstone of diagnosis.

DOI: 10.1530/endoabs.65.CC5

CC6

Severe aortic regurgitation associated with low cumulative dose cabergoline in prolactinoma: a case report

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Background

Cabergoline-associated valvulopathy (CAV) is an established complication of cabergoline therapy in Parkinson's disease, with a definitive echocardiographic triad of severe regurgitation, leaflet thickening, and restricted valve movement without calcification. Long-term cabergoline therapy is deemed safe for prolactinoma due to low dosage. We describe the first UK case report of aortic regurgitation (AR) associated with low-dose cabergoline in prolactinoma.

Case Report

A 67-year-old male with no significant past medical or drug history presented with constipation. Initial investigations demonstrated a T4 of 6.5 pmol/l (normal range, nr, 7–17 pmol/l), and subsequently a prolactin of 79 000 uIu/ml (nr 60–315 uIu/ml). Magnetic resonance imaging of the pituitary revealed a $3.5\times2.4\times2.5$ cm macroadenoma. He was commenced on Cabergoline, initially 1 mg twice weekly but increasing over two months to 2 mg twice weekly. At three months a baseline echocardiogram highlighted mild mitral regurgitation and AR, with aortic valve peak gradient 6.86 mmHg and normal left ventricular (LV) function. His prolactinoma responded well to cabergoline and his dose was reduced to 1.5 mg twice weekly. Three years later he reported mild exertional dyspnoea; his cumulative cabergoline dose was 496 mg. Echocardiogram demonstrated moderate AR. Repeat echocardiogram at six months (cumulative dose 574 mg) showed severe AR with characteristically thickened leaflets and the absence of calcification. Ejection fraction was preserved (65–70%) with normal LV function. Cabergoline was stopped and quinagolide commenced. Two subsequent echocardiograms showed stabilisation of AR without progression of symptoms.

Discussion

The echocardiographic signs and rapid disease progression confirm this case report as only the second demonstrating AR-type CAV in prolactinoma. Notably, AR occurred at a low cumulative cabergoline dose. Given recent Society for Endocrinology guidelines, we emphasise the importance of echocardiogram screening for patients commencing cabergoline for prolactinoma, and thorough assessment for symptoms of CAV at follow-up prior to the recommended five-year repeat echocardiogram.

DOI: 10.1530/endoabs.65.CC6

CC7

Arg798Ter BRIP-1 mutation associated with metastatic phaeochromocytoma

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Case

A 69 year old gentleman with a past medical history of essential hypertension presented to medical services with symptoms of weight loss, muscle weakness and fatigue. Following blood tests, a CT scan, liver biopsy and biochemical screening, a metastatic phaeochromocytoma was diagnosed. He was commenced on alpha and beta blockade. Further imaging, including a MIBG scan, showed non-resectable disease therefore he underwent therapeutic MIBG treatment. Following a good response, he underwent a debulking laparoscopic left adrenalectomy and tissue was sent to the 100 000 Genome Project. Further therapeutic MIBG was planned but unfortunately his disease progressed significantly and he succumbed to his illness. His family history revealed members with breast and ovarian cancer. As part of his routine clinical care, he was referred for genetic testing. Standard testing for inherited causes of phaeochromocytoma were negative however the genetic analysis from the 100 000 Genome Project revealed a variant in the BRIP1 gene c.2392C>T p.(Arg798Ter).

Discussion

The BRCA-1 interacting protein 1 gene (BRIP-1, also known as BRCA-1 associated c-terminal helicase 1, OMIM:605882) is located on chromosome 17q23.2 and encodes the BRIP-1 protein which is part of the DEAH helicase family and is involved in the DNA repair of the BRCA-1 gene. BRIP-1 mutations are known to be associated with the development of breast and ovarian cancer, as well as Fanconi anaemia, however we believe this is the first reported case of a BRIP-1 mutation being associated with metastatic phaeochromocytoma. Following the discovery of this mutation, members of his family have been invited to undergo genetic screening to further define their risk. This case highlights the importance of referring patients with phaeochromocytoma and paraganglioma for genetic testing to help identify new genetic aberrations that may be associated with these conditions and could be the target of new precision medicines.

DOI: 10.1530/endoabs.65.CC7

CC8

Well-differentiated grade 3 neuroendocrine tumors (G3NET) – single centre experience from the UK

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Introduction
The WHO classification distinguishes G3NET as a separate entity. Literature on G3NETs is limited to case-reports and small case-series. We aimed to characterise G3NETs from a large tertiary centre.
Methods
Retrospective analysis from NET database: 2012–2019. All referrals are discussed at a specialist NET-MDT before entry into clinical pathway. Core NET-MDT consists of a radiologist, nuclear-medicine radiologist, histopathologist, specialist-nurses, gastroenterologist, oncologist, endocrinologist, and liver surgeons. Imaging and biochemistry is performed every 6 months or as clinically indicated.
Results
40 G3NETs were identified, with complete data available for 22 at the time of this abstract. Mean(s.d.) age was 69.18(11.1) years (6 females, 16 males). 36.3%(8/22) had undetectable primary, 13.6%(3/22) pancreatic, 13.6%(3/22) small bowel, remaining were colonic, gastric, lung and rectal primary tumours. Median: Ki67 – 30%, range: 25–60% 12/16 had positive or equivocal somatostatin-receptor(SSR) status on imaging. 1 Rectal NET and 3 with undetectable primary had negative SSR imaging. Chromogrannin-A(CGA) and CGB were elevated in 18/22 different patients with mean(s.d.) of 644.592(592.80) pmol/l and 722.45(735.61) pmol/l respectively. Urine HIAA was elevated in 17/22 with mean(s.d.) of 819(813.23). 5/22 had normal levels of all tumor-markers (2 colonic, 1 rectal, 1 unknown and 1 pancreatic). 10/22 received Somatostatin-analogues(SSA): all SSR positive with at-least one elevated tumor-marker. There was no significant change in tumor-marker after SSA. 9/22 received chemotherapy (5/22 capecitabine + temazolamide, 3/22 carboplatin + etopiside, 1 everolimus, 1 FOLFIRI). 5/22 had both SSA & chemotherapy. 0 received PRRT. Of 16 deaths (69.5%), mean length of survival after referral was 15.6 months. Survival >6 months was associated with chemotherapy +/− SSA treatment.
Conclusion
Data from one of UK's largest specialist NET centres, show G3NETs have high mortality with variable tumor behaviour. G3NETs should be managed in specialist centres with NET-MDT expertise.

DOI: 10.1530/endoabs.65.CC8

CC9

A novel inherited epigenetic cause of pseudohypoparathyroidism type 1b

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Pseudohypoparathyroidism type 1b (PHPT1b) is a rare disorder due to resistance to parathyroid hormone (PTH) and subsequent hypocalcaemia, hyperphosphataemia and normal or raised PTH levels. Sufferers usually present in childhood with seizures or tetany due to hypocalcaemia. Typically, PHPT1b is associated with defects on the long-arm of chromosome 20 in the form of uniparental (paternal) disomy of 20q or genetic mutations or sporadic epigenetic changes in *GNAS gene*. Genomic imprinting is well recognised to influence the inheritance pattern of PHPT1b as only maternal versions of the gene are expressed in offspring[1]. Our patient represented in 2014, having been lost to follow-up, with the following biochemistry: Corrected Calcium 2.00 mmol/l (2.20–2.60 mmol/l); Phosphate 1.46 mmol/l (0.80–1.45 mmol/l); 'spot' urinary calcium:creatinine 0.39 and PTH 978 ng/l (14–72 ng/l consistent with her previously held diagnosis of PHPT1b. We consider her an index case for what has eventually been identified as a family of three affected siblings. Although initial genetic assessments in our patient's childhood was unremarkable, reassessment in 2016 revealed a novel pattern of hypomethylation to the maternal 20q region affecting GNAS-AS, GNAS-XL and GNAS-ex1a common amongst all three siblings. No microdeletions were found and uniparental (paternal) disomy was also excluded. This epigenetic defect has caused down-regulation in the function of the GNAS gene subsequently leading to the typical pseudohypoparathyroidism type 1b phenotype. This is the first report of a case of an epigenetic cause for PHPT1b following a familial pattern, although sporadic epigenetic cases are well recognised[2]. The exact epigenetic origin in this family is yet to be identified.
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DOI: 10.1530/endoabs.65.CC9

CC10

Cognitive impairment reversed by cinacalcet administration in primary hyperparathyroidism: a case report

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An 87 year old lady with a background of longstanding cognitive impairment was referred to our service with biochemical evidence of primary hyperparathyroidism. The patient had past medical history of type 2 diabetes mellitus, osteoporosis, hypothyroidism, ischaemic heart disease and primary hyperparathyroidism (under observation in a neighbouring health board). There was no pharmacological cause for cognitive impairment identified. Following acute admission after a fall with increased confusion her calcium was re-checked. Calcium was 3.23 mmol/l with an inappropriately non-suppressed corresponding PTH of 11.4 pmol/l. 25 hydroxy-vitamin D was 55 nmol/l. Renal function and other bloods including thyroid function tests were unremarkable. Hypercalcaemia was initially treated with IV fluids. This lady had previously been diagnosed with cognitive impairment with significant functional impact on her life. She was under the care of the old age psychiatry team. Calcium had been found to be elevated at the time of initial diagnosis with cognitive impairment, however it had consistently been only mildly raised and on account of her co-morbidities, no intervention had been undertaken other than intermittent blood monitoring. The patient was dependent on daily carers, was doubly incontinent and required help with all self-care. This was attributed to cognitive decline secondary to dementia. The patient was commenced on cinacalcet 30 mg twice daily as her calcium had consistently been above 3 mmol/l during her admission. On review at the outpatient clinic 4 months following commencement of cinacalcet, serum calcium had normalised to 2.30 mmol/l. The patient no longer had carers, was no longer incontinent and had become self-caring again. Her daughter reported that her mother was now independently doing her own housework and that her memory impairment had entirely resolved. This interesting case suggests cinacalcet should be considered in patients with cognitive impairment and inoperable primary hyperparathyroidism.

DOI: 10.1530/endoabs.65.CC10

Poster Presentations

Adrenal and Cardiovascular

P1

Single cell RNA-seq reveals complex processing of glucocorticoid controlled transcriptional programmes

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Synthetic glucocorticoids (Gc) are the most potent anti-inflammatory agents known and are widely used to treat a range of chronic inflammatory diseases including rheumatoid arthritis and asthma. However their therapeutic utility is limited by the development of Gc resistance over time – particularly at sites of inflammation. Understanding the underlying mechanisms that control Gc sensitivity is essential to overcome this. Previous studies have measured the average transcriptional response across cell populations, however less is known about how individual cells within a population process Gc signals. Two simple models can explain dose dependent increases in Gc responses at a single cell level:

- the transcriptional response is binary, where a cell either responds or not, and that increasing the dose of Gc simply recruits more responding cells.
- all cells within a population respond to Gc, but individual genes behave like rheostats where the response in each cell is variable and increases a dose dependent manner.

To investigate this, we have completed single cell RNA-seq to measure transcriptomes of 800 individual Gc treated cells. We identify over 500 Gc controlled transcripts, which display dose dependent responses. Surprisingly, these genes separate into two distinct groups, explained by either the binary or rheostat models. We have confirmed our findings using single molecule RNA FiSH, and analysed the impact of inflammatory cues. We find that the magnitude and type of response is gene specific, determined in part by the expression of the Gc receptor (GR), the number of regulatory GR binding sites and the expression of additional intrinsic factors. We therefore uncover a complex regulatory mechanism, controlling gene specific Gc responses in individual cells. This is the first critical step in understanding how inherent transcriptional heterogeneity may underly development of Gc resistance in inflammatory disease.

DOI: 10.1530/endoabs.65.P1

P2

11β-HSD1 mediates muscle atrophy induced by glucocorticoid therapy in chronic inflammatory disease

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Objective
Therapeutic glucocorticoids (GCs) are used to treat chronic inflammatory disease, due to their anti-inflammatory effects. Despite their efficacy, chronic exposure to GCs elicits undesirable side effects, including muscle atrophy. 11 beta-hydroxysteroid dehydrogenase 1 (11β-HSD1) activates GCs within muscle, is induced by inflammation, and has previously shown to drive GC-induced muscle wasting. We examined the role of 11β-HSD1 in mediating muscle wasting in chronic inflammatory disease when treated with therapeutic GCs.
Methods
Muscle biopsies were taken from patients with osteoarthritis (OA) or rheumatoid arthritis (RA). Cortisol production in the muscle was measured using thin-layer chromatography (TLC), and catabolic and inflammatory gene expression assessed. Global 11β-HSD1 knock out (KO) animals were crossed onto the TNF-tg murine model of polyarthritis and received vehicle or corticosterone (100 μg/ml) over 3 weeks in drinking water. Muscles were histologically assessed, and anabolic, catabolic and inflammatory gene and protein expression were examined by RT-qPCR and western blot. WT and 11β-HSD1/KO murine muscle cultures were exposed to TNFα, dehydrocorticosterone or both. Catabolic and inflammatory gene expression was measured.
Results
Cortisol activation in muscle was increased in RA patients than OA patients, and correlated with serum CRP levels. Local inflammation (IL-6 mRNA) was increased in RA compared to OA, correlated with 11β-HSD1, and was accompanied by elevated *Mstn* and *FoxO1* expression. The myopathy previously described in TNF-tg and TNF-tg$^{11\beta\text{-HSD1KO}}$ mice, was aggravated by therapeutic GCs in TNF-Tg mice based on reduced muscle weights and fibre size, while their TNF-tg$^{11\beta\text{-HSD1KO}}$ were protected from muscle wasting. This was accompanied by an attenuated GC-induced elevation of *FoxO1, Trim63* and *Fbxo32* mRNA abundance, and alterations in FoxO1 and ribosomal S6 phosphorylation. These data were in part recapitulated in primary muscle cultures. Together, these data suggest that 11β-HSD1 inhibition may protect against therapeutic GC-induced muscle wasting in chronic inflammatory disease.

DOI: 10.1530/endoabs.65.P2

P3

A role for salivary cortisol measurement in assessing heat tolerance during exercise

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Introduction
Exercise in the heat can impose significant physiological strain and may result in incapacity, illness and death from exertional heat stroke (EHS). The adrenocortical response to exercise is known to be amplified with concurrent heat stress, suggesting the potential utility of cortisol measurement in dynamic surveillance for heat intolerance. In laboratory conditions, a standard Heat Tolerance Assessment (HTA) may be used to determine thermal tolerance to exercise-heat stress. How cortisol responses vary with HTA and whether thermal responses can be discriminated by their measurement has not been investigated.
Methods
During morning hours, 16 healthy military volunteers with no prior history of heat illness underwent blood and saliva sampling at rested baseline (PRE) and immediately after maximal oxygen uptake (VO_2max) testing (POST1) and subsequent HTA (POST2). HTA was conducted at 60% of VO_2max in a climate-controlled chamber (ambient temperature 34°C, relative humidity 40%). Core temperature (Tc) was measured by rectally-sited temperature probe. Cortisol was assayed by radioimmunoassay.
Results
There was a significant ($P<0.01$) association between salivary and serum cortisol measures PRE ($r=0.95$), POST1 ($r=0.8$), POST2 ($r=0.92$) and across pooled timepoints ($r=0.85$). Volunteers with Tc response >39.0°C ($n=5$) vs. <39.0°C ($n=11$) during HTA had significantly higher salivary cortisol on completion of exercise (26.31 [30.81, 16.36] vs. 3.97 [3.45, 4.28] nmol.l^{-1}). Salivary cortisol >8.94 nmol.l^{-1} showed 100% sensitivity and 91% specificity for thermal response >39.0°C.
Conclusions
Salivary cortisol correlates highly with serum cortisol in populations exposed occupationally to exercise in the heat. The strength of association is maintained with high intensity (VO_2max testing) and more moderate intensity (HTA) exercise bouts. Discriminating Tc response by salivary cortisol measurement could provide a non-invasive method of risk stratifying and dynamically assessing for EHS in both laboratory and field settings, including athletic competition, recreational activities and military training.

DOI: 10.1530/endoabs.65.P3

P4

Serum estrogens and the sexual dimorphism in heritable and idiopathic pulmonary arterial hypertension (PAH)

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Serum was collected with ethical approval from Vanderbilt Medical Center, USA for blinded analysis between clinical phenotypes; heritable and idiopathic PAH patients

(hPAH $n=13$, 14; iPAH $n=7$, 12) compared to non-PAH control ($n=17$, 17) (female, males, respectively). Quantification of circulating estrogens in human biofluids may reveal insights into disease aetiology but has been hampered through inadequate sensitivity and specificity of immunoassays. Therefore, we developed and applied a liquid chromatography tandem mass spectrometry (LC–MS/MS) method to profile multiple estrogen metabolites in PAH. Results are shown as mean ± S.E.M. with *P*-values following Kruskal–Wallis statistical tests. E2 (23.3 ± 2.5 vs. 15.1 ± 1.5 pg/ml, $P=0.02$) and 16OHE1 (87.3 ± 20.4 vs. 25.8 ± 1.9 pg/ml, $P=0.004$) were elevated in male iPAH patient's vs. controls with a trend also shown toward E1 elevation (41.9 ± 8.0 vs. 24.8 ± 2.4 pg/ml, $P=0.08$). However, in females, only elevations of 16OHE2 were detected (23.6 ± 4.7 vs. 12.2 ± 2.2 pg/ml, $P=0.005$). The estrogen profiles of hPAH patients did not differ from those of non-PAH individuals. Therefore, profiling estrogen metabolism by LC–MS/MS reveals increased circulating levels of specific bioactive estrogens in iPAH but not in hPAH. The exact pattern differed between male and female iPAH, in both cases the pathway of 16 hydroxylation was upregulated generating proliferative metabolites that may underpin the pathobiology of disease.
DOI: 10.1530/endoabs.65.P4

P5

Cardiovascular morbidity is increased in secondary but not primary adrenal failure

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Background
Increased cardiovascular mortality and evidence of atherosclerosis have been reported in patients with pituitary disorders, irrespective of type of pituitary hormone deficiency. However, there are few data on cardiovascular events in patients with secondary adrenal failure due to pituitary disease compared with those who have primary adrenal failure.
Subjects
2052 patients with primary adrenal failure were compared with 20 366 matched controls and 3948 patients with secondary adrenal failure with 39 134 matched controls, in the UK general practitioner database (Clinical Practice Research Datalink; CPRD).
Methods
All participants were followed-up from one of the following: 1987, the date of diagnosis, the GP registration date, or the date at which GP provided standard information, whichever occurred latest. The end of follow-up was the first cardiovascular event, death, de-registering from the GP, or the end of 2017, whichever occurred earliest.
Results
With total follow-up times of 11 738 vs. 118 657 and 21 148 vs. 209 714 person-years for primary and secondary disease respectively, incidence rates relative to their controls (95%CI) for composite cardiovascular events were 26.8 (24.0–29.9) vs. 22.1 (21.3–23.0) and 32.8 (30.4–35.3) vs. 24.7 (24.0–25.4) per 1000 person-years. In primary adrenal failure, the adjusted HR (95%CI) was 1.08 (0.96–1.21) for composite cardiovascular events, 0.99 (0.83–1.19) for ischaemic heart disease, and 1.00 (0.80–1.25) for stroke. In secondary adrenal failure, the adjusted HR (95%CI) was 1.09 (1.01–1.19) for composite cardiovascular events, 0.91 (0.80–1.03) for ischaemic heart disease, and 1.53 (1.34–1.74) for stroke.
Conclusion
Cardiovascular events were increased relative to normal controls in patients with secondary but not primary adrenal failure. The increased rate was mainly due to increased stroke and not ischaemic heart disease. This study does not support the hypothesis that adrenal failure or its replacement play a significant role in the increased cardiovascular disease observed in people with pituitary disease.
DOI: 10.1530/endoabs.65.P5

P6

Monitoring metyrapone therapy for Cushing's syndrome using salivary glucocorticoid measurement by liquid chromatography tandem mass spectrometry (LC–MS/MS)

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Introduction
Late-night salivary cortisol assessment is an important element when investigating suspected Cushing's syndrome (CS). The goal of medical therapy is achieving a mean (of 5 samples during a single day) serum cortisol (serumF) of 150–300 nmol/l (Cushing Day Curve [CDC]). Metyrapone is an 11β-hydroxylase inhibitor elevating levels of 11-deoxycortisol causing conventional immunoassay (IA) to overestimate SerumF; a problem obviated by LC–MS/MS. We sought to establish if salivary glucocorticoids (salivary cortisol [SalF], cortisone [SalE]) have clinical utility in metyrapone-treated CS patients.
Methods
Seventeen (14 female; age-range 24–74 years) patients with CS on metyrapone were studied on 44 occasions: 15 ACTH-dependent (4 ectopic) and 2 ACTH-independent. SerumF with paired SalF and SalE were taken at 5 time-points throughout the day. SerumF was measured by immunoassay (Siemens CentaurXP) and LC–MS/MS. SalE and SalF were measured by LC–MS/MS.
Results
There was close correlation between SerumF and salivary glucocorticoids both for individual samples and for CDC mean values (Table 1). Bland-Altman analysis comparing SerumF-LC–MS/MS to SerumF-IA confirmed a positive bias of 31% for SerumF-IA (*95% CI −3.2 to 64.8%*). In patients treated with metyrapone and hydrocortisone, SalF showed spurious elevation due to oral hydrocortisone contamination (up to 50-fold).

Table 1

	R	*P*
All measurements ($n=220$)		
SerumF v SalF	0.66	<0.0001
SerumF v SalE	0.77	<0.0001
CDC Means ($n=44$)		
SerumF v SalF	0.55	<0.0001
SerumF v SalE	0.72	<0.0001

Conclusion
Our observed relationships between salivary and serum glucocorticoids show their utility in metyrapone treatment monitoring. Furthermore, SalE may be a preferred biomarker due to its resistance to oral hydrocortisone contamination and stronger relationship with SerumF-LC–MS/MS. Immunoassay measurements overestimated SerumF when compared to LC–MS/MS, therefore should be avoided when monitoring metyrapone-treated CS patients. Further work is required to define the salivary glucocorticoid target range for medical therapy.
DOI: 10.1530/endoabs.65.P6

P7

ULTRADIAN adrenal steroid metabolodynamics successfully discriminates pituitary Cushing's disease from healthy normal variation

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Background
Establishing endocrine diagnoses including pituitary Cushing's remains challenging with delayed or misdiagnosis being very costly for both patient and the health care system. A key issue is that standard diagnostic tests are typically single time point, single analyte samples, which do not consider dynamic variation intrinsic to endocrine systems. Having previously demonstrated that free tissue hormones correlate strongly with plasma concentrations, we present a novel diagnostic approach that utilises ambulatory free adrenal steroid metabolodynamics, without the need for blood sampling.
Methods
Clinical diagnosis of pituitary Cushing's disease was established using conventional means (e.g. DST, urine collection, salivary cortisol, inferior petrosal

sinus sampling). Healthy volunteers were recruited for comparison (age 18–68, no current or recent glucocorticoid use). All participants underwent 24-h microdialysis sampling using 20 kDa linear sampling catheters inserted in abdominal subcutaneous tissue. Microdialysate samples were generated every 20 min using our novel U-RHYTHM fraction collector. Measurement of tissue free hormones concentrations in each sample was achieved using LC–MS/MS. Patients with Cushing's disease were sampled prior to primary pituitary surgery, with diagnosis confirmed by histological presence of corticotroph adenoma.
Results
Data is presented from patients with Cushing's disease ($n=6$) and healthy volunteers ($n=47$). Multiple hormones showed dynamic variation over the 24-h sampling period. An algorithm-based model was developed that considered multiple features in the data set including AUC, timing, rhythmicity, interactions and nadir concentrations. The model successfully discriminated all Cushing's disease profiles from healthy normal variation.
Conclusions
We describe a novel method of blood-free ambulatory sampling that successfully discriminates abnormal adrenal metabolodynamics in pituitary Cushing's disease from healthy normal variation. The technique has considerable potential for both diagnosis and monitoring of endocrine conditions. Validation in a larger cohort of both patients and volunteers is now being conducted.
DOI: 10.1530/endoabs.65.P7

P8

Clinical outcomes in adrenocortical carcinoma: evaluation of single and combined prognostic markers in a UK single centre cohort

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Background
Adrenocortical carcinoma (ACC) has an aggressive but variable behaviour. ENSAT tumour stage and Ki67 proliferation index are used to predict clinical outcome but they are limited in distinguishing patients with best outcome. We aimed to investigate the prognostic role of clinical/histopathological parameters alone or in combination according to previously proposed points-based score (mGRAS, Lippert JCEM 2018).
Methods
We assessed 112 patients with histologically-proven ACC recording age, presence of steroid-or mass-related symptoms at diagnosis, ENSAT stage, tumour resection status, Ki67, progression-free survival (PFS), and overall survival (OS). Complete data were available for 72 patients (median age 50yr; 33M:39F; median follow-up 30 months). Each parameter's prognostic value was tested by univariate and multivariate analyses. Additionally, we evaluated the prognostic performance of mGRAS as follows: age (<50yr $=0$; ≥ 50yr $=1$), symptoms (no $=0$; yes $=1$), ENSAT stage (1–2 $=0$; 3 $=1$; 4 $=2$), resection status (R0 $=0$; RX $=1$; R1 $=2$; R2 $=3$), and Ki67 (0–9% $=0$; 10–19% $=1$; $\geq 20\% = 2$ points).
Results
Univariate analysis showed prognostic prediction of PFS employing presence of symptoms (P 0.003, X^2 8.4), ENSAT stage (P <0.001, X^2 32.5), and Ki67 (P 0.02, X^2 7.0). These remained significant at multivariate analysis. ENSAT stage and Ki67 also showed significant impact on OS (P 0.002, X^2 12.2 and P 0.013, X^2 8.6, respectively). The mGRAS score showed superior prognostic stratification by identifying 3 groups with different PFS (median: undefined, 25, and 7 months, respectively, P <0.001, X^2 20.9) and OS (median: undefined, 89, and 21 months, P <0.001, X^2 20.3).
Conclusion
The prognostic performance of the mGRAS score is superior to that of individual clinical/histopathological parameters. This simple score may guide personalised treatment decisions, e.g. the need for adjuvant therapy and monitoring frequency.
DOI: 10.1530/endoabs.65.P8

P9

Exploring diagnostic thresholds for adrenal insufficiency with the new generation Roche cortisol assay

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Introduction
In 2017 the Roche cortisol assay underwent a generation update. The increased specificity of this assay was expected to lower cortisol results by approximately 30%. Based on a local consensus, the 30 min short Synacthen Test (SST) cortisol was lowered from 550 to 420 nmol/l. With the previous assay, a morning cortisol of ≥ 375 nmol/L gave a 99% PPV of an SST 'pass'.
Aims
- To compare the numbers of SSTs and the SST pass rates before and after the introduction of the new assay.
- To establish the morning cortisol threshold likely to predict an SST 'pass'.

Methods
4 years of SST data was analysed from 2015 to 2019, encompassing 2 years before and 2 years after the new assay
Results
Total numbers of SSTs remained stable (634 vs. 663/2 years). A 30 min cortisol of 420 nmol/l resulted in similar 'pass' rates with the new assay to 30 min cortisol of 550 nmol/l with the old assay (71%). A peak response of 380 nmol/l with the new assay gave similar 'pass' rates to a peak of 500 nmol/l with the old assay (76%) and a PPV of 98.5%. To achieve a 99% PPV of passing the SST (based on a peak of ≥ 420 nmol/l with the new assay) morning cortisol was 390 nmol/l.
Conclusion
The more specific cortisol assay has resulted in uncertainty about thresholds for recommending and assessing SSTs. Kline *et al.* (2017) suggested a cut-off of 350 nmol/l for the peak SST response (reflecting the 30% lower cortisol results with the more specific assay). Most centres are using higher thresholds. We need to consider the potential of missing a diagnosis of adrenal insufficiency, best use of resources, and the adverse consequences of long-term steroid therapy for patients with normal pituitary–adrenal axes.
DOI: 10.1530/endoabs.65.P9

P10

Thyroid hormone receptors in the mouse kidney in health and chronic kidney disease

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Introduction
Chronic kidney disease (CKD) is a devastating condition characterised by progressive loss of renal function that leads to end-stage renal disease. In patients with CKD there is increased prevalence of subclinical hypothyroidism. The importance of thyroid hormone (TH) action on kidney development, growth and physiology has been established, however the role of TH on kidney disease progression is not well understood.
Aim
To assess the expression of TH receptors in the healthy and diseased mouse kidney.
Methods
Immunofluorescent staining for TH receptors, TRα and TRβ, alongside renal cell markers (Lotus Tetragonolobus Lectin, proximal tubule; E-Cadherin, distal tubule; Dolichos Biflorus Agglutinin, collecting duct; Cd31, endothelial cells; F4/80, macrophages) was performed on healthy mouse kidneys and kidneys from mice with nephrotoxic serum nephritis, which mimics CKD. TH receptor TRα1 (*Thra1*), TRα2 (*Thra2*) and TRβ1 (*Thrb1*) mRNA levels in healthy and early (day 7) and late (day 21) stage nephrotoxic nephritis mouse kidney tissue homogenates were assessed by qPCR and circulating tri-iodothyronine was quantified by ELISA.
Results
TH receptors, TRα and TRβ, were localised to the renal medulla of the mouse kidney, namely on the apical side of distal tubules and collecting ducts. The localisation of the receptors was not affected by the disease state, but their abundance was significantly affected with increased *Thra1* ($P<0.001$) and

decreased *Thra2* ($P<0.05$) mRNA levels in late stage nephrotoxic nephritis kidneys compared with controls. The concentration of circulating tri-iodothyronine was decreased ($P<0.05$) in mice with late stage nephrotoxic nephritis compared with controls.

Conclusion

The variation in TH receptor expression in health and disease suggests that kidney disease may influence the ability of renal distal tubule and collecting duct cells to respond to THs. Further work is needed to determine how this may influence kidney function.

DOI: 10.1530/endoabs.65.P10

P11

Cosyntropin stimulation test post unilateral adrenalectomy for non-steroid secreting lesions: not all who fail require steroids

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Aim

Recent studies reported a wide range in baseline and peak cortisol responses to surgery. We report the results of cosyntropin stimulation testing following unilateral adrenalectomy for non-steroid secreting lesions.

Methods

Data of 36 patients who underwent cosyntropin stimulation testing on the second day post unilateral adrenalectomy were collected retrospectively. None of the patients had clinical signs of hypercortisolism. No patient received pre- or intraoperative steroids. A stimulated plasma cortisol of $\geq$450 nmol/l at 30 min was regarded as normal (Abbott Architect assay).

Results

The median age was 58 (31–79) years. Preoperatively, 16 (44.44%) patients had a diagnosis of phaeochromocytoma, 12 (33.33%) had primary aldosteronism and 8 (22.22%) had non-functioning lesions. Preoperative overnight dexamethasone suppression test (ONDST) results were available for 29 patients. Morning cortisol post-ONDST was $\leq$50 nmol/l, 51–138 nmol/l and >138 nmol/l in 23 (79.31%), 5 (17.24%) and 1(3.45%) patients respectively. 20 (55.56%) patients achieved a stimulated cortisol $\geq$450 nmol/l at 30 min and 28 (77.78%) at 60 min. Mean baseline cortisol levels were significantly higher in those who passed the cutoff than in those who did not. No difference was observed in age, lesion size, diagnosis, ONDST results or incremental increase of 150 nmol/l from baseline to 30 min. Using a lower cutoff of 375 nmol/l, 28 (77.78%) patients passed at 30 min and 33 (91.67%) at 60 min. However, only one patient required postoperative steroid replacement.

Conclusions

This study shows that using standard dynamic cortisol test cutoffs following unilateral adrenalectomy would label almost one third of patients as adrenally insufficient, most of whom do not require steroid replacement. Therefore, cosyntropin stimulation testing following unilateral adrenalectomy needs to be interpreted in the clinical context taking into account variable cortisol responses, improved cortisol assays and improved surgical techniques.

DOI: 10.1530/endoabs.65.P11

P12

Endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) as an alternative to left sided adrenalectomy in the treatment of primary aldosteronism

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Primary aldosteronism (PA) is the cause of 5–10% of hypertension, surgically curable in patients with unilateral aldosterone-producing adenomas (APAs). However <1% of patients are currently diagnosed and cured. Newer and simpler modalities of diagnosis and treatment are required. The aim of FABULAS (a feasibility study of endoscopic ultrasound-guided ablation as a non-surgical, adrenal sparing treatment for aldosterone-producing adenomas) is to determine in 30 patients with left sided APAs if EUS-RFA is a safe alternative to adrenalectomy. Alpha and beta-blockade will be used to prevent catecholamine crisis during ablation. Safety outcomes include measures of adrenomedullary activation. Efficacy is evaluated by biochemistry, home and clinic BPs, and quantitative PET CT, using 11C-metomidate, at baseline and 6 months post ablation. 6 EUS-RFA procedures have been performed in 4 patients (mean age 67-years). The mean tumour size was 18 mm (range 9–36mm). Plasma metanephrine levels showed no increase during RFA. During the first 48 h of in-patient monitoring, 2 adverse events have been noted: AF in a patient with known paroxysmal AF, and an episode of pyrexia and raised CRP attributed to transient tissue infarction. All patients are between 4 and 16 months post-ablation with no further adverse events noted. There are several retrospective reports of successful percutaneous and retroperitoneal RFA ablation of APAs. FABULAS is the first prospective study, using a minimally invasive endoscopic route. After deliberately cautious, subtotal ablations in the first three patients, complete clinical and biochemical cure was achieved in the fourth. If we find EUS-RFA of left APAs to be safe and effective, this has the potential to revolutionise the future management of PA.

DOI: 10.1530/endoabs.65.P12

P13

Seasonal vaccination and associated steroid management practice in adrenal insufficiency

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Background

Adrenal insufficiency remains a potentially life-threatening condition, necessitating adequate glucocorticoid replacement and appropriate stress-related adjustment to avoid crisis. Flu-like illness is a key precipitant of adrenal crisis. While some authorities recommend annual influenza vaccination for such patients, uptake rates in this population are unknown. Additionally, while seasonal vaccines may lead to minor symptoms in the general population, there are no specific recommendations on steroid management after vaccination for adrenally insufficient patients in current guidelines.

Methods

Outpatients with adrenal insufficiency attending the Endocrinology Service in one tertiary referral centre over 2018/19 were identified at randomly chosen intervals. They were prospectively asked details of influenza and pneumococcal vaccination history and any side-effects or steroid adjustment using a standard proforma. Their outpatient records were then analysed for additional disease related information.

Results

82 patients were identified; 37 male(45.1%), 45 female(54.9%). Median age was 46(IQR = 39–63). 17.1% were classified as primary adrenal insufficiency, 76.8% secondary, 6.1% were on Mitotane. 74 patients were taking hydrocortisone with median daily dose of 20mg. Prednisolone was used for 8 (median dose = 5.1 mg). Median time since diagnosis was 6.5 years. Overall influenza vaccination uptake was 57% (primary = 42.85%, secondary = 63.40%, mitotane = 80%). 19.5% had received the pneumococcal vaccine within 5 years. Of patients who received the influenza vaccine, 8.5% ($n=4$) temporarily altered steroid replacement afterwards; 2 patients due to hypo-adrenal symptoms and 2 as precaution. 37.8% required stress dosing in the preceding year. Seven had documented adrenal crises in the preceding 5 years. 85% of those with recent crises had been vaccinated.

Discussion

Influenza and pneumococcal vaccination uptake in this adrenally insufficient population is suboptimal. Currently, the majority do not stress dose steroids after vaccination. For most of these the vaccine is tolerated without symptoms of adrenal insufficiency. Further education is required regarding appropriate vaccination in this patient group.

DOI: 10.1530/endoabs.65.P13

P14

Adrenal aldosterone and cortisol levels and their concordance with intervention in patients being investigated for primary hyperaldosteronism

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Introduction
Adrenal venous sampling (AVS) is widely used when investigating primary hyperaldosteronism. In this study we reviewed adrenal aldosterone and cortisol values for measurement range and for biochemical concordance with intervention in patients being investigated for aldosterone producing adenoma (APA).
Methods
Retrospective review of AVS procedures performed at our institution during three years (May 2016–May 2019) was conducted. Aldosterone and cortisol levels, biochemical diagnosis and concordance with clinical intervention were recorded. Cortisol levels were measured using Cobas 6000® automated immune-analyzer (Roche Diagnostics, IA, USA). Aldosterone levels were performed using LC–MSMS by a reference laboratory.
Results
A total of 114 patients' reports were reviewed. Half (53.5%) of study patients showed lateralized APA with 65.7% to the left adrenal. Bilateral adrenal hyperplasia (BAH) reported in 40% of patients. Few patients (6.1%) showed either inconclusive findings or had unsuccessful AVS procedures. Pre-analysis dilution of 1:40 was required for cortisol. Patients with biochemical evidence for left (L)APA had lower median aldosterone and cortisol levels (4300 ng/dl and 470.2 (g/dl) compared to patients with right (R)APA (8500 ng/dl and 873.4 (g/dl) respectively. Median aldosterone cortisol ratios were similar at 12.3. Patients with BAH had significantly lower aldosterone, and cortisol ratios when compared with (L)APA (sevenfold lower) and (R)APA (4 fold lower) ($P=0.00$ for all). There was no significant difference ($P=0.165$) between right aldosterone levels and its cortisol ratio compared to patients with RAPA. However, there was significant difference for left values compared to LAPA ($P=0.05$). Discordance was seen in 2 patients with BAH who underwent left adrenalectomy.
Conclusion
Majority of samples had cortisol and aldosterone levels requiring much higher pre-analytical dilutions than recommended. Patients' distribution may reflect of population studied and or referral criteria. Excellent concordance between biochemical diagnosis and clinical intervention was observed.

DOI: 10.1530/endoabs.65.P14

P15

A rare case of cardiac phaeochromocytoma with germline mutation

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Cardiac phaeochromocytomas account for only 1% of all extra-adrenal phaeochromocytomas. We present a rare case, which through a multidisciplinary approach achieved an excellent outcome. A 49-year-old male presented with chest pain. Echocardiography revealed a pericardial mass behind the left atrium and subsequent cardiac angiography confirmed a highly vascular lesion, suspicious for a phaeochromocytoma. Urine and plasma metanephrines were elevated; urine normetadrenaline 10888 nmol/24 h (0-3350), urine 3-methoxytyramine 15716 nmol/24 h (0–2750) and urine metadrenaline 746 nmol/24 h (0–1250). Plasma normetadrenaline 11648 pmol/l (120–1180 pmol/l), metadrenaline 370 pmol/l (80–510 pmol/l), 3-methoxytyramine 4575 pmol/l (0–120 pmol/l) . There was no family history of endocrine disease and no stigmata of MEN or neurofibromatosis but retrospectively the patient gave a two year history of intermittent headache, palpitations and nausea. The 48x35x38mm soft tissue mass posterior to the left atrium was MIBG-avid, 68Ga-DOTATATE-PET showed no adrenal or other extra-adrenal disease. A diagnosis of cardiac phaeochromocytoma was made and the patient commenced oral Phenoxybenzamine including pre-operative in-patient uptitration. The tumour was removed in a two-stage procedure with coiling and embolization of feeder vessels under Phenoxybenzamine blockade followed by conversion to reversible alpha blockade using Doxazosin 4 mg bd in preparation for tumour resection on cardiopulmonary bypass. The patient underwent successful tumour resection seven months after presentation and histology confirmed a phaeochromocytoma with complete excision, staining positive for chromogranin and synaptophysin. Due to his young age and rare presentation genetic testing revealed a SDHC germline mutation and he was referred for genetic counselling. Approximately one third of phaeochromocytomas are due to germline mutations with over twenty-one genes implicated. SDHC mutations are usually associated with head and neck paraganglioma or phaeochromocytomas with noradrenaline, dopamine or silent hormonal profile and low malignancy risk. Our patient remains well though will remain under lifelong endocrine follow up.

DOI: 10.1530/endoabs.65.P15

P16

Abstract withdrawn.

P17

Very high rate of false positive biochemical results when screening for phaeochromocytoma in a large, undifferentiated population with variable indications for testing

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Pheochromocytoma-Paraganglioma (PPGL) is a rare but important tumour with non-specific presentations that overlap with extremely common entities such as anxiety, hypertension, acute illness and episodic 'spells.' Assessment of urine normetanephrine or metanephrine(UNM-M) in real life practice, where PPGL is very rare and PPGL mimics are extremely common, may show overlap in results with loss of specificity depending on the reference range chosen. We performed a retrospective review of all UNM-M performed in a central lab serving Southern Alberta over an 8 year period, encompassing 13 525 unique patients. After excluding pediatric ages and patients with CKD (eGFR $<$ 50 ml/min), there were 12573 unique patients who had 14383 measures of UNM-M. 88 patients (0.7%) had markedly high UNM-M compatible with likely PPGL. However, depending on the age category (in decades), between 10% and 22% of all UNM results were reported to be above the upper reference limit(URL), particularly between ages of 40–60. Less than 3% had elevations in both UNM and UMN. Of those with high UNM, 96% were less than 3 times the URL. We conclude there is an extraordinarily high prevalence of high UNM seen in real life population use of the test. However, the vast majority of high UNM are unlikely to be PPGL given the disease rarity and the massive population sample size of tests performed. This suggests the current laboratory URL may be too low (high sensitivity but poor specificity) and/or that the reference range may not be appropriate to the type of patient that is being screened for PPGL. Depending on the frequency of use of any screening test in a population, if the disease of interest is rare and the specificity of the test is poor, a very high rate of false positive results will be expected.

DOI: 10.1530/endoabs.65.P17

P18

A rare presentation of Cushing's syndrome

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Ectopic adrenocorticotropic hormone (ACTH) production is a rare cause of Cushing's syndrome. It is usually seen with small cell lung cancer, bronchial

carcinoid, or medullary thyroid cancer. Rarely, the source of ectopic ACTH production can be a phaeochromocytoma. A 55 year old gentleman presented to a general physician following an episode of presumed gastroenteritis with vomiting and general malaise. Further episodes of diarrhoea, joint pains and palpitations followed. On examination, he was hypertensive with no obvious features to suggest any endocrinopathy. He was subsequently found to have raised plasma normetanephrines at 3.98 nmol/l (NR <0.71) and metanephrines at 0.69 nmol/l (NR <0.36). An adrenal CT showed a right 3.8 cm adrenal nodule which was subsequently found to be MIBG-avid in keeping with a diagnosis of phaeochromocytoma. He was started on alpha blockade and referred for right adrenalectomy. However, on admission for adrenalectomy, profound hypokalaemia was noted (potassium 2.0 mmol/l) with non-specific ST segment ECG changes. He was also found to have new onset diabetes (capillary blood glucose 28 mmol/l). He reported to have gained weight and his skin had become darker over the course of last four weeks. In view of these findings, he underwent overnight dexamethasone suppression test, which showed non-suppressed cortisol of 1099 nmol/l. Baseline ACTH was 273 ng/l. A preliminary diagnosis of ectopic ACTH secretion from the known right-sided phaeochrmocytoma was made and he was started on metyrapone. Surgery was postponed to the later date. This is a rare but interesting case of presumed ACTH secretion from a phaeochromocytoma presenting with weight gain, hypokalaemia and new onset diabetes. As phaeocromocytomas are adrenal medullary tumours, cortisol hypersecretion is not always routinely excluded preoperatively. However, this case emphasises the importance of investigations for hypercortisolaemia in known phaeocromocytomas in the appropriate clinical setting.

DOI: 10.1530/endoabs.65.P18

P19

Support for adopting a pragmatic approach to adrenal incidentalomas

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Background

Adrenal incidentalomas are discovered unexpectedly and with increasing frequency on cross-sectional imaging acquired for reasons unrelated to adrenal dysfunction. Whilst the majority are non-functioning, literature suggests there is an increased risk of malignancy for adrenal incidentalomas above 4 cm. American guidelines advising resection of all incidentalomas above 4 cm were established without strong evidence whilst European guidelines adopt a more pragmatic approach.

Aim

This clinical audit was conducted to evaluate the appropriateness of current guidelines by looking at the outcome of non-functional adrenal incidentalomas above 4 cm in a UK hospital over a 9 year period.

Method

A list of all patients discussed in the adrenal MDT from 2009 until 2018 was obtained. Patients identified with non-functional incidentalomas >4 cm were included in the analysis. They were classified into 3 categories at the initial MDT (consensus from endocrinologists and radiologists based on CT appearances) – benign, indeterminate and malignant dependent on Hounsfield units, washout studies and presence of aggressive features.

Results

368 patients discussed at the adrenal MDT of whom 21 (6%) had adenomas >4 cm. These 21 patients were categorised into benign (11 patients, 52%), indeterminate (7, 33%) and malignant (3, 15%). There was no correlation between adenoma size and the three categories. 5 patients in the benign cohort underwent follow up imaging with only 1 increasing in size, insignificantly; the remaining 6 have not re-presented. 3 radiological indeterminate incidentalomas were resected and histologically benign, whilst the remaining 4 were followed up with CT or PET within 18 months with no resultant malignant transformation. Malignant lesions were referred to oncology or surgery for follow up (2 metastasis and 1 lymphoma).

Conclusion

1. Local UK data supports European guidelines advising pragmatic management of adrenal incidentaloma above 4 cm.
2. Benign lesions do not require routine follow up.
3. Indeterminate lesions require imaging surveillance but are usually benign.

DOI: 10.1530/endoabs.65.P19

P20

Can short Synacthen tests (SST) be rationalised by establishing a lower baseline cortisol level which will predict SST outcome?

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Aim

Shortage of tetracosactide in the UK has put pressure on clinicians to reduce the number of SST's ordered. Our aim was to establish if a lower baseline cortisol level from the currently accepted cut-off could predict a positive SST outcome. This would aid our Endocrine Department in rationalising use of tetracosactide.

Methods

A retrospective observational study of indications and results of SST's performed in non-critically ill general medical patients who were referred to the Endocrine OPD. 290 SST tests were done between October 2014 to January 2019 of which, 103 were excluded as baseline cortisol was taken after 1000 h. Plasma cortisol was measured at baseline and 30 min following administration of tetracosactide 250 (g. The locally validated assay specific cut-off for passed SST was ≥ 550 nmol/l (Roche Cobas e601 analyser). Receiver operating Characteristic (ROC) curve was generated to determine the predictive value of basal cortisol for a passed SST.

Results

Indications for referral included; establishing a new diagnosis (52%), assessing adrenal axis in patients with other endocrine disorders (37%), assessing safety of stopping long term steroids (10%) and undocumented (1%). 187 SST's were analysed of which 139 (74%) passed and 48 (26%) failed. ROC curve analysis identified that basal cortisol of <130 nmol/l predicted failure with 100% sensitivity and ≥ 400 nmol/l provided 100% specificity to pass SST. Using the minimum ROC distance criterion, basal cortisol value of ≥ 300 nmol/l was identified to predict passing SST with 72% sensitivity and 77% specificity.

Discussion

Our findings suggest that baseline cortisol ≥ 400 nmol/l could have prevented SST's as it predicts failed SST. In this cohort 50 SST's could have been potentially avoided with significant cost saving implications. However, we continue to recommend SST as further studies are needed to validate this baseline cortisol cut-off.

DOI: 10.1530/endoabs.65.P20

P21

Dipeptidyl peptidase-4 inhibitor sitagliptin induces vasorelaxation via the activation of Kv channels and PKA

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The present study investigated the vasorelaxant effects of sitagliptin, which is a dipeptidyl peptidase-4 (DPP-4) inhibitor in aortic rings pre-contracted with phenylephrine (Phe). Sitagliptin induced vasorelaxation in a concentration-dependent manner but the inhibition of voltage-dependent K^+ (Kv) channels by pretreatment with 4-aminopyridine (4-AP) effectively reduced this effect. By contrast, the inhibition of inward rectifier K^+ (Kir) channels by pretreatment with barium (Ba^{2+}), large-conductance calcium (Ca^{2+})-activated K^+ (BK_{Ca}) channels with paxilline, and adenosine triphosphate (ATP)-sensitive K^+ (K_{ATP}) channels with glibenclamide did not change this effect. Although the application of Q21 22536, which is an adenylyl cyclase inhibitor, also did not change this effect, treatment with KT 5720, a protein kinase A (PKA) inhibitor, effectively reduced the vasorelaxant effects of sitagliptin. ODQ, which is a guanylyl cyclase inhibitor, and KT 5823, a protein kinase G (PKG) inhibitor, did not impact the effect. Similarly, the effects of sitagliptin were not altered by eliminating the endothelium, by pretreatment with a nitric oxide (NO) synthase inhibitor (L-NAME), or by inhibition of small-conductance Ca^{2+}- ctivated K^+ channels (SK_{Ca}) using apamin. Furthermore, neither the inhibition of Ca^{2+} channels by retreatment with nifedipine nor the inhibition of sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) pumps by pretreatment with thapsigargin changed the effect. Taken together, these results suggest that sitagliptin induces vasorelaxation by activating PKA and Kv channels independent of PKG signaling pathways, other K^+ channels, Ca^{2+} channels, SERCA pumps, and the endothelium.

DOI: 10.1530/endoabs.65.P21

P22

Linagliptin induces vasorelaxation via inhibition of Rho-associated protein kinase activity in aortic smooth muscle

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In this study, we used the phenylephrine-precontracted aortic ring preparation to investigate the mechanisms underlying the vasorelaxant effect of linagliptin. We found that linagliptin induced vasorelaxation in a dose-dependent manner. The vasorelaxant effect of linagliptin was not changed by the removal of the endothelium, or by pre-treatment with a NO synthase inhibitor (L-NAME) or a small-conductance Ca^{2+}-dependent K^+ channel inhibitor (apamin). Moreover, administration of the adenylyl cyclase inhibitor Q122536, protein kinase A (PKA) inhibitor KT5720, guanylyl cyclase inhibitor ODQ, or protein kinase G (PKG) inhibitor KT5823 did not change the vasorelaxant effect of linagliptin. However, blocking of Rho-associated protein kinase by Y-27632 significantly reduced linagliptin-induced vasorelaxation. Involvement of vascular ion channel in the vasorelaxant effect of linagliptin was also investigated. Pre-treatment with the vascular K^+ channel inhibitors Ba^{2+}, 4-AP, paxilline, and glibenclamide did not affect linagliptin-induced vasorelaxation. Furthermore, the *L*-type Ca^{2+} channel inhibitor, nicardipine, and the SERCA pump inhibitor, cyclic piazonic acid, were not related with the vasorelaxant effect of linagliptin. From these findings, we concluded that linagliptin-induced vasorelaxation was mediated by the inhibition of Rho-associated kinase, but not with the endothelium, PKA or PKG-dependent signaling cascades, vascular K^+ channels, Ca^{2+} channels, or intracellular Ca^{2+}.

DOI: 10.1530/endoabs.65.P22

P23

Non-adrenal tumours encountered during adrenal surgery

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Background
Benign cortical and medullary tumours, adrenocortical cancers (ACC), bilateral adrenal hyperplasia, adrenomyelolipomas and metastases are commonly discussed in the differential diagnosis of a tumour in the adrenal bed. This study reports a series of non-adrenal tumours encountered during surgery for expected adrenal tumours.
Method
Retrospective review of surgical practice in a tertiary referral centre.
Results
Between 2014 and 2018 the annual workload for adrenal surgery ranged 60–75. In this large cohort of over 300 patients, a small minority of patients ($n=15$) had unexpected histological diagnoses. Eight patients with median age 29 years had ganglioneuromas (5R:1L). Five patients with median age 75 years had large retroperitoneal schwanomas initially suspected to be ACC based on PET activity (3R:2L). Two patients age 58 years old with left-sided tumours had a GIST (gastrointestinal stromal tumour) measuring 55 and 150 mm. A 12-cm left adrenal teratoma was excised in a 27 years old woman, a bronchogenic cyst and a hemangioma were diagnosed as left-sided phaeochromocytomas based on mild biochemical abnormalities and positive MIBG uptake.
Conclusion
Retroperitoneal tumours should be considered in the differential diagnosis of non-functional large (adrenal) mass. Ganglioneuromas were more common in younger patients and schwannomas in older patients. Functional imaging with C^{11}-metomidate might become a useful adjunct in differentiating cortical adrenal tumours from other retroperitoneal tumours.

DOI: 10.1530/endoabs.65.P23

P24

Short Synacthen test; are we getting it right?

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Background
The short Synacthen test (SST) is used primarily to diagnose adrenal insufficiency (AI), with hyponatraemia being among the commonest indications. Given the national shortage of tetracosactide and following cases of test mismanagement highlighted by our Biochemistry department, we investigated the indications, appropriate patient selection and performance of this test.
Methods
A retrospective analysis of 117 cases identified to have a SST performed between January 18' to May 18' in our Trust. We triaged the indications of the requests to four categories; Symptoms, Medications, Related conditions and Physical signs.
Results
65% of all indications were based on a single criterion, the most common of which was hyponatraemia (54%). Only 2 cases of hyponatraemia proved to be AI and both met at least one more criterion. Overall, 88 patients had a normal response to SST and 19 patients had abnormal response. Only 2 patients with a single criterion had a positive test confirming AI. 17% of all cases were deemed as an unnecessary request, whilst in 8% the test was not performed correctly. 9% of the tests could have been avoided as they had a satisfactory morning cortisol. We observed a small number of 60 min Cortisol requests ($n=5$), none of which added diagnostic value.
Conclusion
The positive result yield was higher if more than one criteria were met. We conclude that it may be beneficial to perform a 9 am cortisol test prior to requesting SST. The trust is in need of guidelines for ordering SST to assist health care professionals with indications and restrictions.

DOI: 10.1530/endoabs.65.P24

P25

A case of severe hypokalaemia and metabolic acidosis

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Introduction
Hypokalaemia is a common biochemical abnormality seen in inpatients; it is usually mild and iatrogenic. We report a rare case of muscle paralysis due to severe unprovoked hypokalaemia, presenting on acute medical take.
Case
The patient presented with a two week history of epigastric pain, nausea, vomiting, muscle spasms and dizziness. Past medical history included asthma, vitiligo, pernicious anaemia as well as long standing history of unexplained 'collapses'. Possibility of Addison's had been excluded in the past following a short stint of steroid therapy.
Initial Investigations
Serum potassium 2.0 (3.5–5.3 mmol/l), bicarbonate 18 (22–29 mmol/l), Chloride 114 (95–108 mmol/l), ALP 366 (38–126 U/l), ALT 135 (0–50 U/l), random cortisol 273 nmol/l. She was commenced on steroids and intravenous Potassium in the Emergency department. However, a day later she developed breathlessness with progressive paralysis of all limbs ($-4/5$). Consequently she required closed monitoring with repeated potassium infusion via central access. Restoring potassium within normal range resulted in complete neurological recovery. Once stable she was switched to Spironolactone (while aldosterone levels pending) and oral potassium replacement to good effect. Steroids were stopped given an optimal response to Synacthen (peak of 533 nmol/l).
Further investigation
Hyperchloraemic metabolic acidosis with a pH of 7.27, potassium remained low at 1.9 mmol/l, Urinary pH of 7, 24 h urinary potassium excretion of 131(35–90 mmol), anti-adrenal antibodies were negative, aldosterone:renin ratio was 43 (<64), liver ultrasound was unremarkable. The sustained metabolic acidosis, hypokalaemia and urinary pH>5.5 were in-keeping with distal renal tubular acidosis (***dRTA***).
Conclusion
dRTA is a disorder of renal acidification characterized by inability to acidify urine to pH <5.5 despite the presence of systemic metabolic acidosis and hypokalaemia. Hypokalaemia leads to acute onset paralysis and may be a presenting symptom of dRTA. This case report highlights the importance of considering **dRTA** in the differential diagnosis of severe hypokalaemia.

DOI: 10.1530/endoabs.65.P25

P26

A cross-sectional audit reviewing the management of adults with congenital adrenal hyperplasia in Leicester

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Introduction
Following the recent publication of The Endocrine Society Clinical Practice guideline for Congenital Adrenal Hyperplasia (CAH), we performed an evaluation of the service provided for adults with CAH to assess how well we are meeting the guideline standard and to make recommendations for service improvement.
Methods
We performed an audit of adults with CAH under the care of the University Hospitals of Leicester. We undertook a cross-sectional analysis from 1 January 2018 to 31 December 2018. We collected demographic data, treatment regimen, previous surgery for CAH and laboratory biochemical and steroid profiles. Relevant imaging were obtained from PACS. Excel 2013 was used for statistical analysis and graphs.
Results
80 adult patients with CAH were included for analysis, of which 61% ($n=49$) were female and 61% ($n=49$) were Caucasian. 60% ($n=48$), 33% ($n=26$) and 9% ($n=7$) of our cohort were taking Hydrocortisone, Prednisolone or Dexamethasone respectively, and 60% ($n=48$) were taking Fludrocortisone in combination with a glucocorticoid. Two patients had an adrenalectomy. Of the female patients, 21 had undergone vaginoplasty and 15 had undergone clitoral corrective surgery (all prior to coming under our care). 34% ($n=n=27$) and 33% ($n=26$) of our cohort were overweight or obese respectively. Despite this high prevalence, annual HBA1C was only performed in 35% ($n=44$) of cases and annual cholesterol was only tested in 26% ($n=33$) of cases; raised cholesterol remained untreated. Benign adrenal rest tumours were identified in 3 patients. Osteoporosis/osteopenia was confirmed on DEXA scanning in only 2 of our patients.
Discussion
The management of CAH in adult patients varies, in terms of frequency of assessment of clinical and biochemical parameters. Our recommendations: 1) Cholesterol and HbA1c should be tested and treated in at risk individuals. 2) Osteoporosis or osteopenia should be confirmed on DEXA scanning. 3) Weight must be reviewed annually.

DOI: 10.1530/endoabs.65.P26

P27

Secondary hypertension service in a District General Hospital – the success story

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A secondary hypertension service was set up by the Endocrinology team in 2016 aiming to capture young hypertensive (age <30 years), refractory hypertension and hypertensive emergency to provide holistic care. A pathway was developed streaming Hypertensive emergencies to the high dependency area for intravenous treatment and hypertensive urgencies to the Ambulatory care for oral medications. All patients were linked to a secondary hypertension clinic. Staring with one clinic per month, now there are 8 clinics every month due to significant 61% increment of new referrals in 2017 and another 73% in 2018. Care was provided for a total of 215 new patients. About a third of these patients (33.95%) had a secondary cause of hypertension; Primary aldosteronism 28.76%, obstructive sleep apnoea 23.28%, male secondary hypogonadism 10.95%, renal artery stenosis 10.95%, white coat hypertension 12.32% and other causes, e.g. three Adrenal Cushing's, two Acromegaly, one phaeochromocytoma, one vasculitis and three non-compliance. Our prevalence rate was similar to that reported by the European Heart journal in 2014; and in some conditions even higher. An email clinic was introduced for dose adjustment based on home blood pressure logs. This ensured patient safety, saved GP appointments and increased the capacity for new slots by reducing follow up visits. 87 admissions were avoided saving 435 bed days and £71 775. Innovative ideas, inspirational team work, supportive management, structured pathway and continued education were key to the success of setting up this unique service in our District General Hospital.

DOI: 10.1530/endoabs.65.P27

P28

Recalibration of thinking about adrenocortical function assessment: How the random cortisol relates to the short Synacthen test 'Verdict'

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Background
The short synacthen test (SST) is the most commonly performed investigation to assess for suspected adrenocortical dysfunction. We investigated how random cortisol levels may relate to pass/fail on the STT.
Methods
We analysed the relation between random cortisol measurements taken between 04.40 and 20.52 in the day and results of SST baseline and 30/60 min cortisol performed over a 12 month period (338 SSTs) at Salford Royal Hospital. Serum cortisol was measured on the Siemens Centaur Autoanalyser (Erlangen, Germany). A 30/60 minute cortisol of ≥ 500 nmol/l in the presence of a baseline of ≥ 200 nmoll was taken as a 'pass'. Failure of cortisol to reach 350 nmol/l post-Synacthen was taken as a definite fail.
Results
The findings indicate that a random cortisol level of ≥ 195nmol/l is associated with a 'pass' on the STT in 100% of cases. A random cortisol level of 95 nmol/l or less was associated with a 'fail' on the STT in 100% of cases. Overall there was no significant relation between random cortisol and 30 min post-Synacthen cortisol. In relation to the agreed 'pass' cut off post-Synacthen of cortisol ≥ 500 nmol/l, in 8.5% of cases the 60 min cortisol was ≥ 500 nmol/l but 30 min cortisol was below. Thus the 60 min cortisol indicated adequate adrenocortical function. In 0.5% of cases the converse was true. For a definite fail of cortisol <350 nmol/l there was disagreement between 30 and 60 min cortisol in 10 cases. In 30% of these cases the 60 minute cortisol was ≥ 350 nmol/l but the 30 min cortisol was below 350 nmol/l. In other words.
Conclusion
Our findings suggest that in the if the random cortisol level is ≥ 195 nmol/l, there may be no need to perform a SST unless specific evaluation is required. In 8.3% of cases an adequate cortisol response was seen at 60 min but not at 30 min. The 60 min cortisol therefore retains utility.

DOI: 10.1530/endoabs.65.P28

P29

Immunoassay interferences and their impact on patient care

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Hormones and other analytes that are requested in the investigation of endocrine abnormalities are routinely measured using automated immunoassays in clinical laboratories. Assay kit inserts usually detail interference in terms of % cross reactivity, but this information is not always communicated to the clinician. Another complicating factor is that different assay platforms show different degrees of interference, therefore clinicians need to be aware of the source of their patients' results. UK NEQAS is an NHS External Quality Assessment provider of clinical specimens available for clinical laboratories. This allows laboratories to have confidence in the quality of the results that they provide to their users. UK NEQAS is uniquely placed to challenge the different analytical platforms with the same specimen and UK NEQAS prides itself in also providing an educational service which shares and improves knowledge. This poster explores a number of well-known drug interferences in immunoassays across different analytical platforms; for example prednisolone and metyrapone in cortisol assays, norethisterone in testosterone assays and biotin in immunoassays in general. Prednisolone is known to cross react in Cortisol immunoassays and we show at a therapeutic concentration of prednisolone, the % cross reactivity ranges from 55% in the Siemens ADVIA Centaur cortisol assay, compared to 6% in the Roche Gen II cortisol assay. All the most commonly used immunoassays are all affected to some degree. There are cases where not all immunoassays are affected; these include 11-Deoxycortisol interference (Metyrapone blocks cortisol biosynthesis and leads to an increase in circulating 11-Deoxycortisol levels), Norethisterone interference in testosterone assays and Biotin interference in immunoassays.

Strong relationships between the laboratory and the clinician allow communication of this vital information to allow clinicians to more appropriately review their patients' results.

DOI: 10.1530/endoabs.65.P29

P30

A UK national audit of the laboratory investigation of phaeochromocytoma and paraganglioma

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Background
A range of laboratory tests are available for investigation of phaeochromocytoma/paraganglioma (PPGL) and there is scope for significant variation in practice between centres. Endocrine Society Clinical Practice Guidelines make recommendations concerning the laboratory investigation of PPGL. We performed a national audit using these recommendations as audit standards.
Methodology
A questionnaire was distributed to all clinical biochemistry departments in the UK, who were encouraged to complete this with advice from endocrinology colleagues where required. The 21 questions included were designed to compare each centres practice to recommendations in the Endocrine Society guideline concerning the laboratory investigation of PPGL.
Results
58 centres responded to the survey. Some of the key findings include: 95% of centres meet the recommendation that plasma or urine metanephrines (UMETs/PMETs) are included as part of first line testing. However, there are 12 different combinations of tests in use for biochemical testing indicating that different protocols are employed. All laboratories measuring metanephrines use either LC–MS/MS or LC-ECD methods as recommended. There is significant variation in patient preparation before sampling for PMETs. For example, 28% of centres take PMETs samples only in seated patients, 14% supine only and 40% supine or seated in different situations (e.g. supine for borderline seated results). There are variations in the reference ranges used in different centres that could cause significant differences in interpretation (there is an up to twofold difference in the upper limits for UMETs for example).
Discussion
There is significant variation in the laboratory investigation of PPGL across different centres in the UK. The results of this audit highlight areas where practice may be improved and could inform further work on standardising the approach to investigating PPGL. Collaboration between the UK Endocrinology and Clinical Biochemistry communities will likely be required to address the findings of this audit.

DOI: 10.1530/endoabs.65.P30

P31

The PASS score is not a reliable measure of predicting aggressive potential in phaeochromocytoma – experience over 14 years at our University Teaching Hospital

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Background
The phaeochromocytoma of the adrenal gland scaled score (PASS) is used for histological reporting of phaeochromocytomas as a surrogate marker of malignant potential. A PASS score of ≥ 4 (of a maximum of 20) suggests an aggressive tumour and hence the importance of lifelong careful follow-up. However, the utility of the PASS score has been questioned recently due to the discordance between PASS score and clinical outcomes.
Aim
To review the PASS score in all patients who have undergone adrenalectomy at our unit over the last 14 years and review its usefulness in predicted aggressive/malignant potential.
Methods
We searched for patients who had undergone an adrenalectomy at our University Teaching Hospital between 1 July 2007 and 30 April 2019 using clinical codes and filtered those with histologically confirmed phaeochromocytoma. Basic demographic data, PASS score, clinical outcomes and duration of follow up were recorded.
Results
40 patients were identified with an equal male:female split. One patient underwent bilateral adrenalectomy for bilateral phaeochromocytomas. Mean age at diagnosis was 56.2 years (range 22–82). Mean tumour size was 5.8 cm (range 1.7–13). Onepatient had a PASS score of >15 who had metastatic disease at presentation. Three patients experienced recurrence of the phaeochromocytoma (one local, 2 distal) between 2 and 8 years after their adrenalectomy. All had a PASS score of 3. PASS score for the remaining 37 patients ranged between 0 and 8 with no evidence of recurrence of their disease so far.
Discussion
In our experience, the PASS score does not accurately predict the malignant or aggressive potential of phaeochromocytomas, in line with similar findings in the literature. Tumour heterogeneity and histological sampling may be contributing factors. Therefore, our clinical practice is to monitor all patients lifelong with regular clinical assessment and metanephrine measurement. There is a need for more accurate biomarkers to help predict recurrence and malignant potential.

DOI: 10.1530/endoabs.65.P31

P32

An unusual case of adrenal cortical carcinoma presenting with hypogonadotrophic hypogonadism

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We report the case of a 52 year old gentleman who presented to Primary Care with a short history of gynaecomastia, loss of libido and erectile dysfunction. He was normally fit and well, with no past medical history and no regular medications. Initial blood tests showed low testosterone (0.7 nmol/l (normal 11–28)) with inappropriately low gonadotrophins (LH 1.2iU/l (1.5–9.3), FSH $<$0.1 iU/l (1.4–18.1)). Other blood tests were unremarkable (TFTs, prolactin, FBC and U&Es). A diagnosis of hypogonadotrophic hypogonadism was made. However, in view of gynaecomastia, an oestradiol level was added on later. This was significantly elevated at 932 pmol/l (28–156). Following these results, the gentleman was referred to Endocrinology. Repeat bloods confirmed both hypogonadotrophic hypogonadism and hyperoestrogenaemia. MRI of the adrenal glands demonstrated a right sided well-circumscribed supra-renal mass measuring 8 cm x 8 cm. CT scan excluded distant metastases. Other blood tests revealed normal plasma metanephrines, aldosterone, plasma renin activity, cortisol, gut hormones, overnight dexamethasone suppression test, DHEAS, androstenedione and 17OH-progesterone. The MDT determined this gentleman was likely to have an oestrogen-secreting adrenal tumour and he underwent right open adrenalectomy. Post-operatively, the gynaecomastia resolved and he noted rapidly improved libido and energy levels. Four weeks after surgery, bloods demonstrated normalisation of the oestradiol (151 pmol/l) ($<$150) and testosterone (19 nmol/l (8–30)). Histology demonstrated adrenal cortical carcinoma (ACC) pT3Nx Ki-67 60%. There were also tumour cells present at the margins, thus adjuvant chemotherapy with mitotane was initiated. ACC is rare, with an annual incidence of 1–2 per 1 million. Specifically, feminising adrenal tumours such as in this case, account for less than 2% of all cases. Typical presenting features are demonstrated here with gynaecomastia, loss of libido and erectile dysfunction. Additionally, this case demonstrates the importance of checking oestradiol levels in cases of hypogonadotrophic hypogonadism where the cause is unclear.

DOI: 10.1530/endoabs.65.P32

P33

Aldosterone deficiency type 1 due to mutation of the CYP11B2

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Isolated hyperreninemic hypoaldosteronism presents in infancy with failure to thrive, hyponatremia, hyperkalemia, markedly elevated plasma renin activity, and low or inappropriately normal aldosterone. It is usually caused by mutations in the CYP11B2 gene encoding aldosterone synthase. Patients have normal cortisol levels and no features of congenital adrenal hyperplasia. We report a patient who presented with hyperreninemic hypoaldosteronism in early infancy.
Case Report
A 38 years old presented on the 18th day of her birth with hyponatremia, hyperkalemia, dehydration and failure to thrive. Chromosomal analysis confirmed a normal female karyotype of 46, XX. She had normal cortisol and 17-hydroxyprogesterone levels by cosyntropin stimulation testing and normal ACTH levels. She had high plasma renin activity, low aldosterone level, and elevated 18-hydroxycorticosterone, compatible with type 2 aldosterone synthase deficiency. The patient was heterozygous for a novel *CYP11B2* mutation: c. 1157C > A (p.Val 386Ala). She was treated with fludrocortisone and has been symptomatic. She delivered a healthy baby girl last year.
Discussion
Salt-wasting forms of congenital adrenal hyperplasia are relatively common causes of hyperreninemic hypoaldosteronism. Aldosterone regulates electrolytes and deficiency results in hyponatremia, hypovolemia, and hyperkalemia. Plasma renin activity (PRA) is elevated. Aldosterone synthase is a mitochondrial cytochrome P450 enzyme, CYP11B2. It is encoded by the CYP11B2 gene located on chromosome 8. Most patients with aldosterone synthase deficiency carry inactivating mutations in CYP11B2 gene. It is an autosomal recessive disorder, presenting with severe salt-losing in early infancy usually at the age of 1–2 months with diarrhea, failure to thrive, severe dehydration and no virilisation. Plasma electrolytes show. Patients have hyponatremia, hyperkalemia, and acidosis with normal cortisol response and elevated plasma renin activity with low aldosterone levels. All respond to fludrocortisone treatment. Our case illustrates the clinical significance to recognize this condition as it has a good long-term prognosis when adequate fludrocortisone replacement is instituted.

DOI: 10.1530/endoabs.65.P33

P34

Hepatocellular carcinoma masquerading as an adrenocortico-carcinoma

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Case
A 62 year old man was admitted acutely with right sided abdominal pain. A CT scan with contrast showed an acute right-sided adrenal haemorrhage with adjacent necrotic lymphadenopathy and multiple pulmonary nodules. An MRI, requested to further define the lesion, reported a malignant looking 7.4 cm right adrenal mass with direct focal invasion into the liver and inferior vena cava however no further liver lesions were identified. The images were discussed at the multi-disciplinary meeting (MDT) and it was thought that this was most likely a metastatic adrenocortico-carcinoma (ACC). Adrenal biochemical functional testing was performed which all returned normal. His lesions were not amenable to surgical treatment. Biopsies of ACC are not usually recommended due to bleeding risk and tumour cell seeding therefore a referral was made for consideration of palliative mitotane. Whilst awaiting this, an FDG-PET was performed to further define the extent of his disease. This showed more malignant deposits: multiple areas in the liver, lung, lymph nodes and possibly bone. This led us to re-think the diagnosis and, following re-discussion in the MDT, a lymph node biopsy was performed. Histology confirmed metastatic hepatocellular carcinoma (HCC) as opposed to ACC. Alpha feto-protein subsequently sent was 280Ku/l (0–10).
Discussion
Patients presenting with large adrenal lesions and metastatic deposits can present a diagnostic and management dilemma. Radiological investigations can be strongly suggestive of a primary adrenocortico-carcinoma however there are no clear guidelines as to when to biopsy metastatic lesions associated with large adrenal masses unless there is a known separate primary cancer, with biopsies of primary adrenal lesions discouraged entirely. However in some circumstances, a biopsy can be helpful in confirming a diagnosis to ensure correct management. This case adds to the small number of reported cases where adrenal metastatic HCC deposits have caused a diagnostic challenge.

DOI: 10.1530/endoabs.65.P34

P35

Mitiglinide induces vasodilatory through the activation of voltage-gated K+ channels and SERCA pump in aortic smooth muscle

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The vasodilatory effects of the meglitinide class of anti-diabetic drug, mitiglinide in phenylephrine (Phe)-pre-contracted aortic rings were investigated. Mitiglinide concentration-dependently induced vasodilation. Administration of the large-conductance Ca^{2+}-dependent K^+ (BK_{Ca}) channel inhibitor paxilline, inward rectifier K^+ (Kir) channel inhibitor Ba^{2+}, and ATP-dependent K^+ (K_{ATP}) channel inhibitor glibencalmide did not affect the vasodilatory effect of mitiglinide. However, application of the voltage-dependent K^+ (Kv) channel inhibitor 4-AP, effectively reduced mitiglinide-induced vasodilation. Although pre-treatment with the Ca^{2+} channel inhibitor nicardipine did not change the mitiglinide-induced vasodilation, pre-treatment with the SERCA pump inhibitor cyclopiazonic acid and thapsigargin reduced the vasodilatory effect of mitiglinide. In addition, the vasodilatory effect of mitiglinide was not changed by the blockers of adenylyl cyclase, guanylyl cyclase, protein kinase A, or protein kinase G. Removal of the endothelium and inhibition of endothelium-dependent vasodilatory mechanisms also did not affect the vasodilatory effect of mitiglinide. Based on these results, we suggested that mitiglinide induces vasodilation via activation of SERCA pump and Kv channels. However, the vasodilatory effects of mitiglinide did not related with other Ca^{2+} channels, K^+ channels, PKA/PKG signaling pathways, or the endothelium.

DOI: 10.1530/endoabs.65.P35

P36

Extensive resection of adrenal tumours requiring complex multidisciplinary approach

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Aims
Given that the vast majority of surgeons who undertake adrenal surgery in UK have a median workload of 1 case/year there is increasing awareness that the care of such patients should be centralised. This case series illustrates the benefits of multidisciplinary input from surgeons with various expertise involved in the care of complex adrenal cases.
Methods
Retrospective review of cases in which endocrine, hepatobiliary and cardiac surgeons collaborated.
Results
During 2008–2017 the median annual workload for adrenal surgery in our unit was 65 cases/year (range 52–75). Veno-venous cardiac bypass was used in seven patients with tumour thrombus extending in the supradiaphragmatic inferior vena cava (IVC). A patient operated in 2007 remains disease free (32yrs, Cushing syndrome, left adrenal tumour with thrombus into the atrium). Median survival was 3 years. There was one in-hospital death (day 11 postop due to hypoxic brain injury and multi-organ failure. Hypothermic cardiorespiratory arrest was used for two patients: i. 12-cm right-sided non-secreting adrenocortical carcinoma excised in continuity with a 5-cm segment of IVC followed by IVC reconstruction; ii. 16-cm malignant right phaeochromocytoma extending into right atrium. Both patients are alive at over 5 years after operation. Patients with infrahepatic IVC tumours extension ($n = 11$) were operated without establishing cardiac bypass. Support from the cardiac team was provided during adrenalectomy of five patients with phaeochromocytomas and severe catecholaminergic-induced heart-failure. Similar multidisciplinary approach was used for two patients with IVC sarcoma and Ewing's sarcoma of the adrenal gland in whom a complete en-block resection of tumour and segment of IVC was achieved.
Conclusion
Multidisciplinary surgical collaboration is needed for a minority of patients with locally-advanced adrenal tumours who can achieve favourable oncological outcomes.

DOI: 10.1530/endoabs.65.P36

P37

Group education clinics for patients with adrenal insufficiency; a DGH experience

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Background

Adrenal crisis is a potentially life-threatening situation which can affect any patient with adrenal insufficiency (AI). Patients with AI and healthcare professionals looking after them should know the sick day rules and when and how to use parenteral hydrocortisone. Patient stories and feedback from patients with AI indicated low standards locally. We therefore aimed to empower patients through education and provide them with a hydrocortisone emergency kit.

Method

Patients with known AI were invited to a group education session run by an endocrinologist and pharmacist to discuss their condition, 'sick day rules', training on when and how to administer IM hydrocortisone and were supplied with an emergency kit containing everything to administer that injection. A maximum of 12 patients were invited to each session.

Results

Since February 2019 29 patients, mean age 55 years old (range 19–73), have attended the sessions and were provided with education, leaflet on sick day rules, link to patient website, educational material and an emergency kit. Patient feedback from the session rated the sessions between 1 (unsatisfactory) and 5 (very good), the average rating was 4.8, Some patients had never had an emergency hydrocortisone kit, some did not know the sick day rules. Many patients reported concern about lack of awareness of the severity of adrenal insufficiency amongst medical professionals, especially in emergency situations.

Discussion

Feedback has been extremely positive with patients feeling more confident on sick day rules and how to use emergency hydrocortisone. Patients were actively encouraged to request additional doses of hydrocortisone if they felt they needed it in emergency situations. Education sessions for the emergency department doctors, advanced clinical practitioners and junior doctors have been started as a result of this.

DOI: 10.1530/endoabs.65.P37

P38

Audit of adrenal crisis management at University Hospitals Leicester NHS Trust

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Background

Adrenal crisis is a life threatening emergency with an incidence of 5–10 adrenal crises/100 patient-years with mortality around 0.5/100 patient-years.

Objective

Audit of inpatient adrenal crisis management was undertaken in line with Society for Endocrinology (SFE) guidance 2016 (Trust audit No:9763).

Methods

Retrospective evaluation of electronic and paper case records of 2 years (January 2017–December 2018).

Results

Over 2-year period, 34 adrenal crises episodes in 25 patients ($n = 25$; 13 M: 14 F) were identified. Mean age = 50 years; mean length of stay = 7 days. Hyponatraemia noted in 13/25 (52%); hyperkalaemia in 11/25 (44%). 19/25 (72%) received intravenous hydrocortisone; 25/25 (100%) steroid doses doubled. 24/25 (96%) were under Endocrine outpatient care; 12/25 (48%) received endocrine inpatient input. 2/25 (8%) died of malignancy; none from adrenal crisis (Table 1).

Table 1

SFE guidance	Compliance
IV Hydrocortisone	18/25 (72%)
IV fluids	23/25 (92%)
Endocrine input	12/25 (48%)
Tapering steroid dose instruction	23/25 (92%)
Endocrinology outpatient follow-up	25/25 (100%)
Emergency hydrocortisone kit	21/25 (84%)
Medic-alert device advice	5/25 (20%)
Steroid Emergency Card	21/25 (84%)
Patient education leaflets, website etc	0% recorded in notes
Doubling of steroids	25/25 (100%)

Discussion

Although compliant in majority of measures, suboptimal management was noted in providing inpatient endocrine input, patient information dissemination, medic alert advice etc. Following interventions were undertaken:

1. Adrenal crisis Trust guideline in accordance with SFE was introduced (1).
2. Electronic prescribing alert of intravenous hydrocortisone and doubling of steroids was inserted to remind clinicians, similar to Newcastle upon Tyne model (2).
3. Electronic alert of steroid-dependent patients upon admission is currently underway.

Learning point

We feel that clinician awareness is vital for optimal management of adrenal crisis. Electronic prescription alert of emergency steroid management as well as electronic steroid dependent patient alert at the point of admission will aid reduce morbidity and potentially mortality.

DOI: 10.1530/endoabs.65.P38

P39

Retrospective analysis of the management of adrenal incidentalomas

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Introduction

With the increased use of imaging modalities, detection of Adrenal Incidentaloma (AI) has become common.

Aim

We evaluated management of patients with AI to improve service delivery.

Method

Patients with AI referred to our endocrinology outpatient service (2006–2019). Data was collected from electronic case records and radiology reporting system. Demography, biochemical investigations, time interval between two scans, size of the adenoma, increase in size on the second scan and reported Hounsfield units (HU) with washout period were analyzed.

Results

49 patients studied (male-19, female-30) with average age 66 years (range 40–86). Median size of adenoma – 2.2 cm (range 0.7–4.3). In this cohort, 40(81%) had repeat scan, 3(6%) currently awaiting, 5(10%) – not repeated on radiologist based on adenoma characteristics and 2(4%) died before scan was performed. Interval between two scans was 24 months (2 months–13 years). 5(10.2%) of patients had increase in size on the second scan and average increase by 0.2 cm (0.0–0.2 cm). HU and washout period were reported only in 6(12%) of first scan and 12(24%) of second scan. 24-h urine catecholamines and renin:aldosterone ratio performed in 18(36.7%), overnight dexamethasone suppression test (ODST) performed in 20(40%) patients.

Conclusion

There was no consistency in the time interval between two scans and radiology reporting of tumor characteristics. Although 24-h urine catecholamines were performed in all patients, ODST was performed in minority. Implementing appropriate biochemical investigations and standard radiological reporting based on the European Society of Endocrinology guidelines will facilitate propitious management and discharge of patients. This will improve the delivery of care and

reduce significant burden on an endocrinology service in a district general hospital setting. Radiology reporting with precise characterization of an adenoma is an important determinant in the management plan. We intend to create awareness amongst our radiology colleagues to standardize reporting.

DOI: 10.1530/endoabs.65.P39

P40

The peri-operative management of diabetes in elective major vascular procedures: a completed cycle quality improvement project (QIP)

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Aim

Diabetes is the most common metabolic disorder in the UK, affecting 20–30% of vascular inpatients. Diabetes is associated with increased mortality and adverse outcomes. Major vascular operations accompany an increased incidence of metabolic complications. There are trust guidelines outlining the optimal peri-operative management of diabetes. We audited compliance to this guideline in patients undergoing major vascular operations and measured patient outcomes.

Methods

Retrospective data analysis was performed on diabetic patients undergoing major elective vascular operations between July and December 2018. Adherence to the trust guideline was analysed in terms of pre-operative assessment, medication changes, diabetes team referrals, prescription and use of variable rate insulin infusion (VRII). The intervention was departmental teaching in January. The second cycle was undertaken between January and May 2019.

Results

Thirty-five patients made up the first cycle, of which 20(57%) had HBA1C measured and 2(6%) had their diabetes control optimised in the pre-operative clinic. Of the total 35 patients, 4(11%) had inappropriate medications modifications, 7(20%) were inappropriately referred to the diabetes team and VRII was inappropriately initiated or prescribed in 3(9%) of these. The second cycle consisted of 46 patients. Thirty-five (76%) had their HBA1C measured pre-operatively, with 5(11%) of them referred to their general practitioner for diabetes optimisation. Medications were inappropriately modified in 4(9%) of patients, with 4(9%) inappropriate referrals to the diabetes team. VRII was inappropriately prescribed or initiated in 2(4%) of patients.

Conclusion

An improved peri-operative management of diabetes was seen post intervention. There was improved preoperative optimisation of diabetes. Doctors prescribed medications and VRII more appropriately. The rate of inappropriate diabetes referrals was reduced, streamlining diabetes resources. We showed that simple interventions, such as departmental teaching, can increase awareness among teams and lead to improved outcomes. This intervention can be applied to other surgical specialties.

DOI: 10.1530/endoabs.65.P40

P41

Use of sub-cutaneous pump for continuous hydrocortisone administration in patient with bilateral adrenalectomy and small bowel injury complicated by enterocutaneous fistula

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We present a case of 39y old male who underwent adrenalectomy and aortic lymph node dissection for neuroendocrine tumour in context of underlying VHL disease and previous adrenalectomy. Iatrogenic injury to his duodenum resulted in prolonged, multiple intraabdominal infections and development of enterocutaneous fistula. He had to remain NBM, relied on high dose iv hydrocortisone administration and TPN feed for several months. Conversion back to oral steroids was considered unreliable (tablets observed in fistula drainage bag) and resulted in adrenal crises. To facilitate self-care and discharge for home convalescence prior to stage 2 surgery to close EC fistula, continuous hydrocortisone delivery via sc pump was commenced using a Medtronic 640G insulin pump with mio infusion set. The pump reservoir was filled with 50 mg/ml hydrocortisone solution (100 mg Solucortef powder diluted with water for injection). 3 ml reservoir contained 150 mg of Hydrocortisone (1 pump 'unit' of solution contained 0.5 mg of Hydrocortisone). The pump was set to delivery 60mg of hydrocortisone/24 h in immediate recovery and the dose was gradually reduced to 32 mg/24 h. This dose had to be increased further to 48.5 mg/24 h which ensured serum cortisol concentrations between 226 and 427 nmol/l during 2-hourly cortisol profiling. Separate Basal 2 profile (double the routine dose = 97 mg/24 h) was set for period of illness.

Discussion

The main challenge was complexity of reservoir filling. After intensive training the patient managed this, and the method was well received. In these exceptional circumstances, sc continuous hydrocortisone delivery proved to be reliable, leading to reduction in dose and resolution of signs of steroid over-treatment. It allowed a very complex patient to be discharged. The plan is to proceed to stage 2 surgery to close fistula, which will hopefully allow return to normal bowel functioning and return to oral hydrocortisone administration.

DOI: 10.1530/endoabs.65.P41

P42

A rare presentation of an androgen-secreting tumour without hyperandrogenic symptoms

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A 33-year-old lady was referred to the endocrinology clinic with mild hyperprolactinaemia on the background of having missed a single period, with a raised testosterone of 4.1 nmol/l (0–2). She had no other medical problems. Her menstrual cycles normalised by the time she attended clinic. She had no galactorrhoea, visual disturbance or features of hyperandrogenism. Her BMI was normal and she was normotensive. Blood tests revealed mild hyperprolactinaemia of 709 nU/l (100–500), which normalised to 243 nU/l post-cannulation, confirming stress hyperprolactinaemia. However, a raised dehydroepiandrosterone sulphate (DHEAS) of 24.5 umol/l (0.7–11.) was also noted. Testosterone was normal on repeat measurement (1.7 nmol/l). Oestradiol, SHBG, TFTs, FSH, LH, and 17-OHP were all normal. Repeated DHEAS throughout her menstrual cycle remained elevated (17.6–20.4 umol/l) and adrenal imaging was therefore undertaken. CT adrenals revealed a 2.1 cm lesion in the right adrenal gland with concerning features (pre-contrast HU44). An overnight dexamethasone suppression test demonstrated a suppressed cortisol (<28 nmol/l), but an unsuppressed DHEAS (20.4 umol/l). Plasma metanephrines and a pelvic ultrasound were normal. 24-h urine steroid profile showed elevation in two androgen metabolites: aetiocholanolone-5 β 1930 ug/24 h (270–1390) and androstenetriol 740 ug/24 h (100–250), but overall the results were not typical of a biochemically active adrenocortical carcinoma. MDT recommended surgery based on the concerning radiological features. She underwent a right retro-peritoneoscopic adrenalectomy. Her DHEAS normalised (10 umol/l) by day 1 post-op. Histology demonstrated a Weiss criteria score of 2 with no clear capsular invasion suggesting an adrenal neoplasm of uncertain malignant potential.

Discussion

Pure DHEAS-secreting tumours are very rare and typically present with hirsutism and virilisation in >90% of patients. However, here we present an androgen-secreting tumour in the absence of clinical symptoms or signs of hyperandrogenism, but with a previous one-off raised testosterone level. Thus, this case demonstrates that the absence of androgenic symptoms cannot exclude the presence of these DHEAS-secreting tumours.

DOI: 10.1530/endoabs.65.P42

P43

An unusual pathology presenting as adrenal incidentaloma

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Introduction
Adrenal Incidentalomas (AI) are frequently encountered in clinical practice with radiological studies suggesting a frequency of 3% at 50 years rising to 10% in elderly. Majority of AI are non functional adenomas with malignant lesions quoted as less than 20% at most. We report a case of AI, which was found to a Melanoma on biopsy with no other primary site.
Case
An 84 year old gentleman was found to have a right suprarenal mass on ultrasound done for lower urinary tract symptoms. He was physically very fit and well and his past medical history included Benign prostatic hypertrophy, Glaucoma and Osteoarthritis. He underwent a CT which showed a 6.3 cm right adrenal mass with possible spread to right lung hilum. His case was discussed in the MDT and a biopsy of this lesion showed a Melanoma. He underwent dermatological assessment including biopsies, which did not pick up any melanoma. Endocrine workup showed the lesion was non-functional. Our current working diagnosis is a Primary adrenal melanoma (PAM) and he is undergoing Immunotherapy.
Discussion
Primary adrenal melanomas are rare entities with only about a couple of dozen reported in history. It has been suggested that they may arise from ectopic melanocytes from pluripotent neural crest cells. PAMs are usually larger, unilateral and asymptomatic. Our case underwent a biopsy due to the larger size and the coexistence of a hilar lesion. Carsten's *et al.* proposed a criterion (unilateral, no history of melanomas, no removal of pigmented skin or eye lesions) to distinguish PAM from metastatic lesions. The main modalities of treatment include surgical resection with targeted therapy and immunotherapy. Survival rates are poor and mortality after surgery has been quoted as 100% within 2 years.

DOI: 10.1530/endoabs.65.P43

P44

A case of catecholamine induced cardiomyopathy

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Introduction
We describe the case of a patient referred to Cardiology with an abnormal ECG & hypertension. Investigation led to the diagnosis of catecholamine induced cardiomyopathy caused by a pheochromocytoma. The case is unique as the cardiomyopathy was reversed with alpha and beta blockade prior to surgery.
Case
A 56 year old female with 20 pack year smoking history, no regular medications and evidence of hypertension underwent CT AP for abdominal pain which revealed bilateral adrenal incidentalomas. Investigations revealed raised urine metanephrines 9538 nmol/24 h(ULN 4400 nmol/24 h) and SPECT scan confirmed bilateral phaeochromocytoma. ECG on presentation demonstrated sinus rhythm with evidence of LVH, peaked p waves (lead III), with inverted p waves in I, aVL and V1–V3. Echocardiographic evaluation of her heart demonstrated severe LV dysfunction with no significant valve disease. A diagnosis of Catecholamine induced cardiomyopathy was made. The patient was treated with Doxazosin MR 8 mg tds and Atenolol 25 mg bd preoperatively and her ECG was repeated, which confirmed resolution of the conduction abnormalities previously observed.
Conclusion
Phaeochromocytoma is a rare but significant cause of myocardial dysfunction. Excessive catecholamine release is associated with changes in cardiac muscle structure, resulting in alterations in cardiac function. ECG changes, especially those consistent with LVH, ST changes and QTc prolongation have been commonly cited in patients with phaechromocytoma. P wave changes, associated with atrial hypertrophy are a less commonly observed marker of catecholamine excess. Case series have reported ECG normalization of treated patients, hence ECG evaluation may be an important marker of successful medical as well as surgical management of phaeochromocytomas.

DOI: 10.1530/endoabs.65.P44

P45

An audit of the management of adults with Congenital Adrenal Hyperplasia in Newcastle upon Tyne – where are we now?

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Background
Congenital adrenal hyperplasia (CAH) is the commonest genetic endocrine disorder, affecting 1 in 18 000 UK births. The 2010 CaHASE Study identified a myriad of health problems associated with CAH and its treatment, and a lack of consensus on treatment strategies in adults. Endocrine Society guidelines (2010, revised 2018) have since been published to support management. As one of the original CaHASE centres, we have audited our recent practice against these new standards.
Methods
Data was collected retrospectively from online records available from 2014 to February 2019. Patients with a diagnosis of CAH attending our hospital were identified through coding. Only those with a diagnosis of classical 21-hydroxylase deficiency were included. Local approvals were obtained.
Results
24 patients were included (15F, 9M; mean age 38.8 years, range 21–76). 8 patients were treated with hydrocortisone, 3 with dexamethasone, 4 with prednisolone and 9 with a combination. The average hydrocortisone equivalent dose was 21.7 mg (6.7–46 mg). Only 42% of patients underwent recommended biochemical testing at their last clinic visit. On the basis of androstenedione and 17-hydroxyprogesterone recommendations, 37.5% appeared undertreated, 12.5% overtreated, and 12.5% around target. There was electronic documentation of blood pressure in 75%, and BMI in 17%. 79% and 58% underwent screening for diabetes and hyperlipidaemia respectively. 62.5% of patients had undergone bone densitometry (20% osteoporotic, 40% osteopenic). Although only 56% of males underwent testicular ultrasound, 80% of these had evidence of adrenal rest tissue. Whilst 96% of patients had sick day education, only 54% had evidence of parenteral steroid provision.
Recommendations
CAH is a complex condition and patients require careful monitoring and tailoring of treatment. We have found that complication rates in the patient cohort studied were high. Having identified some areas for improvement we plan to develop a clinic proforma to streamline and improve patient care.

DOI: 10.1530/endoabs.65.P45

P46

Primary adrenal failure from bilateral adrenal infiltration by classical Hodgkin's lymphoma

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Lymphoma can cause adrenal glands infiltration, but only a handful of cases of adrenal involvement have been reported in classical Hodgkin's lymphoma. We present a case of 24y male of Indian origin presenting with B symptoms, AKI, breathlessness, and diarrhoea. CT CAP showed lymphadenopathy, enlarged kidneys and adrenal glands bilaterally. ^{18}F-FDG PET CT showed PET avid lymphadenopathy and non-avid bilateral adrenal masses. Histology of axillary lymph node confirmed classical Hodgkin's lymphoma possibly of nodular sclerosing subtype. Chemotherapy was commenced. Before 2nd cycle developed hypotension and unretractable vomiting. This was thought to be related to chemotherapy, but it did not respond to numerous antiemetics. Significant skin, gums, tongue pigmentations that intensified over 2 month period were noted. Eventually he was found to have adrenal failure and Hydrocortisone and Fludrocortisone were commenced with significant improvement in his symptoms.
Results
ACTH – 2543 ng/l, cortisol 76 nmol/l, SST baseline, 30 min, 60 min – 86, 79, 78 nmol/l respectively, Na 131 nmol/l, K 5.1 nmol/l. Adrenal antibodies and Quantiferon TB Gold were negative excluding Addison's disease and tuberculosis. ^{18}F-FDG PET CT post 2 cycles of chemotherapy demonstrated resolution of FDG avidity in lymph nodes and reduction in size of adrenal masses with prominent FDG uptake, which was not evident at pre-treatment scan.
Discussion
Bilateral adrenal involvement with adrenal failure in classical Hodgkin's lymphoma appears to be very rare, but needs to be considered especially in context of enlarged adrenals at presentation and refractory vomiting during

chemotherapy. Rapid appearance of pigmentation in this case suggests rapid destruction of adrenal cortex by the disease. Hyperpigmentation may be challenging cosmetically and culturally and can be missed in darker skin patients. Photographic comparison can be useful in diagnosis. This patient was much paler on his photos 2 months prior diagnosis.

DOI: 10.1530/endoabs.65.P46

P47

Hypokalaemic cardiac arrest – a rare presentation of primary aldosteronism

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A 58 year old female, with a 15 year history of hypertension and recent poor control, was admitted to the emergency department after an out of hospital cardiac arrest due to ventricular fibrillation requiring DC cardioversion. Initial investigations showed a metabolic alkalosis with profound hypokalaemia at 1.7 mmol/l. In view of lateral ST depression on the ECG post-resuscitation, she underwent an urgent coronary angiogram which demonstrated unobstructed coronary arteries. Whilst in intensive care, she required several days of intravenous potassium replacement and remained hypertensive with systolic blood pressures of 170 mmHg. An enquiry of her GP records revealed that she had been commenced on Indapamide MR two weeks prior to her presentation. Her potassium levels in the last three years had been between 2.9 and 3.4 mmol/l. She had been on amlodipine and ramipril for many years. During the admission, she was switched to Doxazosin and Verapamil MR and oral potassium replacement. A subsequent saline suppression test twelve days after presentation confirmed primary aldosteronism with baseline aldosterone of 430 pmol/l and fully suppressed plasma renin activity <0.2 nmol/l per hour (aldosterone renin ratio >2150) and 4-h aldosterone of 440 pmol/l. An adrenal CT revealed a 2.8 cm left adrenal lesion with low Hounsfield units consistent with a lipid-rich adenoma. Plasma metanephrines and overnight dexamethasone suppression test were normal. She remains well and is currently awaiting selective adrenal vein sampling (AVS) and will be considered for adrenalectomy if confirmed localisation on AVS. Hypokalaemia is common in primary aldosteronism. However, arrhythmias and cardiac arrest are rare and are thought be secondary to an additional trigger. We believe that introduction of a thiazide like diuretic in our patient led to severe hypokalaemia and ventricular fibrillation. Screening for primary aldosteronism should be considered in patients with hypertension and hypokalaemia.

DOI: 10.1530/endoabs.65.P47

P48

Twenty-five years of familial glucocorticoid deficiency: genotypic and phenotypic variability

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Within the last 25 years more than 400 cases with suspected Familial Glucocorticoid Deficiency (FGD) have been referred to our centre for genetic testing. All cases had low or undetectable serum cortisol paired with an elevated plasma ACTH level. Our patient cohort comprises 352 families from 30 different nationalities and ranges from neonates to patients in their eighties. In 1993 the first gene defect, in *MC2R,* was discovered by candidate gene sequencing. Subsequently 8 further genes have been identified in our cohort by Next Generation Sequencing technologies, in temporal order; *MRAP*, *STAR*, *MCM4*, *NNT*, *TXNRD2*, *SGPL1* and *CYP11A1*. *MC2R* mutations account for 25% of cases, *MRAP* for 20%, *NNT* for 8%, *STAR* for 7%, *CYP11A1* for 3% and *MCM4*, *TXNRD2* and *SGPL1* each for 1%. These genes are involved in diverse pathways with phenotypes resulting from defective ACTH signalling, cholesterol transport, steroidogenesis, cellular redox homeostasis, DNA replication or sphingolipid metabolism. Functional assays of the proteins these genes encode, have provided some explanation for the variability of the phenotype and association(s) with other co-morbidities. The work has highlighted non-classical presentations of lipoid congenital adrenal hyperplasia and P450 side-chain-cleavage enzyme deficiency with partial loss-of-function variants in *STAR* and *CYP11A1* respectively. In addition, a few cases have revealed syndromic disease exemplified by the *MCM4* variant causing natural killer (NK) cell and glucocorticoid deficiency with DNA repair defect and *SGPL1* mutations which cause a syndrome of primary adrenal insufficiency, progressive renal dysfunction plus in some cases ichthyosis, acanthosis, immunodeficiency and neurologic defects. The finding of further gene defects; novel genetic aetiologies, Copy Number Variation or non-coding variation in known genes will improve the diagnosis for the 40% of patients presenting with FGD who currently have no genetic cause identified.

DOI: 10.1530/endoabs.65.P48

P49

An interesting case of acute hypoadrenalism following an intervention to treat bleeding splenic artery pseudoaneurysm by thrombin injection

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Background
Evidence shows relative adrenal insufficiency is one of the complications known to be associated with major procedures such as cardiopulmonary bypass surgery or critical illness. This is the first case we are presenting someone with acute hypoadrenalism following post thrombin injection to treat pheudoaneurysms.
Case
We present an interesting case of 55 years old man with known decompensated alcoholic liver disease with oesophageal varices, portal hypertension and chronic pancreatitis, admitted with haematemesis and melena, initially requiring resuscitation with intravenous fluids, terlipressin, blood transfusions and tranexamic acid. Gastroscopy showed hypertensive gastropathy. CT angiography was organised for ongoing haemetemesis which confirmed the increase in the size of his known pseudoaneurysm in the distal part of the splenic artery from 14 to 28 mm, compressing the posterior wall of stomach. This was treated by interventional radiology team with percutaneous CT guided thrombin injection in to the splenic artery pseudoaneurysm. Immediately post procedure he became haemodynamically unstable with hypotension, hypoglycaemia and his sodium dropped initially to 124 and then to 111 mmol/l just within 24 h requiring hypertonic saline to treat the acute hyponatremia. He was managed on intensive care for haemodynamic instability. With morning cortisol of 88 mmol/mol he was commenced on hydrocortisone following which he showed dramatic improvement. He had normal pituitary profile and normal adrenal and pituitary imaging. He had an uneventful recovery and was discharged home on regular hydrocortisone replacement and subsequent assessment showed recovery of hypothalamic- pituitary and adrenal axis and he was weaned off steroids eventually.
Conclusion
Complication of acute hypoadrenalism following major interventional procedures is uncommon. Ischaemia related to prolonged hypotension or the acute vascular spasm is some of the reasons hypothesised. This is the first case report of hypoadrenalism following thrombin injection to treat pseudoaneurysm.

DOI: 10.1530/endoabs.65.P49

P50

Vildagliptin induces vasorelaxation by activation of SERCA pump and Kv channels in aortic smooth muscle

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In this study, we explored vildagliptin-induced vasorelaxation and its related signaling mechanisms using phenylephrine induced pre-contracted rabbit aortic rings. Vildagliptin induced vasorelaxation in a dose-dependent fashion. Pre-treatment with the large-conductance Ca^{2+}-dependent K^+ channel inhibitor paxilline, ATP-dependent K^+ channel inhibitor glibenclamide and inward rectifier K^+ channel inhibitor Ba^{2+} did not change the vasorelaxant effects of

vildagliptin. However, administration of the voltage-gated K+ (Kv) channel inhibitor 4-aminopyridine significantly decreased the vasorelaxant effects of vildagliptin. In addition, application of two SERCA inhibitors, cyclopiazonic acid or thapsigargin, effectively reduced the vasorelaxant effects of vildagliptin. These vasorelaxant effects were not changed by pretreatment with adenylyl cyclase, guanylyl cyclase, protein kinase A (PKA), or protein kinase G (PKG) inhibitors, or by elimination of the endothelium. Based on these results, we suggested that vildagliptin induced vasorelaxation via activation of the SERCA pump and Kv channels. However, PKA/PKG-related signaling pathways associated with vascular relaxation, other K^+ channels, and the endothelium was not related in vildagliptin-induced vasorelaxation.

DOI: 10.1530/endoabs.65.P50

P51

Heparin-induced hypo-aldosteronism and hyperkalemia

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We present an interesting case of Heparin inducedhypoaldosteronism associated hyperkalemia in a 69 year old man with a prosthetic heart valve requiring a right sided nephrectomy for a liposarcoma. His persistent hyperkalaemia failed to respond to conventional treatment initiallybut a switch to Warfarin and use of oral Fludrocortisone was effective in normalisation of observed high renin and low aldosterone levels. Early and timely recognition of Heparin induced hypoaldosteronism associated hyperkalemia remains a challenge especially in busy acute care settings. Heparin induced hyperkalaemia can be a life-threatening emergency. Early recognition of hyperkalaemia can improve patients' outcomes. We present a case which highlights the importance of assessing risk benefit ratio at time of initiating heparin therapy which can be associated with persistent hyperkalemia due to underlying hypoaldosteronism. We present a man in his sixties with a past medical history of type 2 diabetes mellitus (T2DM) and mechanical aortic valve prosthesis requiring regular anti coagulation with Warfarin. He presented with a large abdominal mass and his CAT imaging revealed an underlying retro peritoneal tumour which was later confirmed on further histology. His diabetes medications included Metformin and Gliclazide. His Warfarin was discontinued pre operatively and Tinzapirin was commenced post-surgery but had to be discontinued due to hemi-peritoneum and bowel perforation. It was observed that his serum K was elevated on day 5 post LMWH initiation. His ECG showed no hyperkalaemic changes. From above discussion, we advocate that high degree of suspicion needs to be exercised for recognising potentially life-threatening and reversible condition like hyperkalaemia associated with hypoaldosteronism. Clinicians should be aware that hyperkalaemia could be caused by low molecular weight Heparin especially in multi-morbid surgical patients, where bleeding and thrombotic risks need to be assessed. A multi disciplinary approach is necessary for optimal therapy in this clinical scenario.

DOI: 10.1530/endoabs.65.P51

P52

Inpatient pheo crisis in neurofibromatosis type1 (NF 1) 'Triggers and management'

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Pheochromocytoma crises are uncommon but have high mortality. We describe herein a case where multidisciplinary team management was crucial in safely carrying the patient through such a crisis. The patient was a 63 year old lady with a background of neurofibromatosis type 1 (NF-1), and previous renal artery stenosis bypass surgery. She was admitted via A&E with increasingly frequent episodes of sweating, headache, dyspnoea and palpitations. Her troponin was raised at admission at 72 ng/l, progressively rising to 364 ng/l . CT pulmonary angiogram revealed a 6 cm left sided adrenal mass with cystic features. In view of her background diagnosis, the possibility of pheochromocytoma was raised at an early point (confirmed later by elevated metadrenaline at 5834 pmol/l and normetadrenaline at 4198 pmol/l). She was placed on doxazosin for alpha blockade with a view to introducing beta blockade at a later point. Subsequently she developed a narrow complex tachycardia which was treated with amiodarone, and chest pain which was treated with morphine and metoclopramide. She was sent for a coronary angiogram which revealed unobstructed coronary arteries. At this point she developed a broad complex tachycardia (recurrent VT) and uncontrolled hypertension at 254/112 mmHg. This patient was moved to ITU, and given Mg sulphate infusion, phenoxybenzamine and verapamil. With the Mg sulphate, her condition stabilized, and her BP regressed to normal at 136/89. She was discharged within a few days, stably established on phenoxybenzamine and verapamil and is awaiting surgery for her tumor.

Learning points

1. Triggers for this crisis included the intra-arterial use of contrast and the use of metoclopramide.
2. The troponin rises were likely indicative of coronary artery vasospasm due to the catecholamine surges.
3. Prompt initiation of emergency treatment including Mg sulphate is essential.
4. Early involvement of ITU is crucial to management of such patients.

DOI: 10.1530/endoabs.65.P52

P53

Adrenal suppression following Herbal remedy for Nasal Polyps....not to be sniffed at

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A 69-year-old South Asian male presented in A+E with hyponatremia. He had pervious history of Lyme Node TB (treated 2014), Asthma and Nasal Polyps. Medication history, patient was taking Fludrocortisone nasal spray for the 30–40 years and Seretide inhaler. Also, CT scans at admission did not identify relapse in Lyme Node TB. Upon investigation he was found to have undetectable morning cortisol (<28 mmols). He was started on Hydrocortisone 10 mg, 5 mg and 5 mg regime, patient denied any symptoms associated with secondary adrenal insufficiency and referred to the Endocrinologist. He underwent a Short Synacthen Test off his Seretide inhaler and Fluticasone nasal spray, the cortisol peeked at 72 mmols and ACTH <5 mmols. LFT's, U+E's and thyroid function where in normal limits. Upon further detailed history patient was admitted on taking a 'herbal' powdered preparation by sniffing it up his nose for the last 7–8 years which he believed helped him with his nasal polyps/blocked nose. The yellow powder was sent off to toxicology. Toxicology analysis showed the presence of theophylline, chlorpheniramine, paracetamol, bromhexine, diclofenac, prednisolone and many more. Patient was advised to discontinue the herbal preparation we believe this contributed to the cause of Secondary Adrenal Insufficiency. Despite the fact patient was taking steroid longs term patient did not have any Cushingiod features. A DEXA scan was booked to rule out osteoporosis due to long term steroid use. In conclusion a comprehensive drug history should be taken when diagnosing patients considering herbal medication despite the discontinuation prescribed steroid medication.

DOI: 10.1530/endoabs.65.P53

P54

A case of adrenal insufficiency due to histoplasmosis

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A 75 year old male presented in August 2017 with dizziness, nausea and weight loss. In ENT clinic he was found to have right vocal cord lesion. He had CT chest, abdomen and pelvis which showed mediastinal and hilar lymphadenopathy and bilateral adrenal lesions. A PET–CT scan showed intense metabolic uptake in the adrenals with low volume, but moderately active mediastinum and hilar lymphadenopathy. He was presumed to have adrenal and mediastinal Tuberculosis and was started on anti-tuberculosis medications. He had postural hypotension and moderate hyponatraemia and had Short Synacthen Test which sowed baseline cortisol of 364 but post tetracosactide cortisol inceased very mildly to 377 and 392 after 30 and 60 min respectively. He had further extensive investigations and adrenal biopsy showed necrotising granuloma which was negative for TB culture and PCR. Fungal stain suggested fungal spores (PAS stain positive for fungal spores, although cryptococcal Ag negative). Pan fungal PCR result from fungal reference lab was positive for Histoplasma Capsulata, and later

culture was also positive for Histoplasma. He was started on treatment of disseminated Histoplasmosis with two weeks of IV ambisome, loaded on itraconazole, and then started on oral itraconazole. Keeping in view postural hypotension, hyponatraemia and flat response to Short Synacthen Test, hydrocortisone and fludrocortisone were started. Postural hypotension and hyponatraemia resolved and Fludrocortisone was withdrawn successfully. He had Short Synacthen Test after one year with baseline cortisol of 148, 30 min post tetracosactide cortisol 157 and 60 min cortisol was 161, indicative of permanent adrenal failure. CT chest, abdomen and pelvis repeated after 18 months of treatment which showed mild improvement in mediastinal lymphadenopathy but adrenal lesions significantly improved. Patient continues to be on Itraconazole and hydrocortisone and is clinically doing very well and is currently asymptomatic.

DOI: 10.1530/endoabs.65.P54

P55

Unexplained adrenal insufficiency after gastric bypass surgery

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Introduction

Gastric bypass surgery is performed for intractable severe reflux oesophagitis not amenable to vagotomy and pyloroplasty. Long-term complications include dumping syndrome, nutritional deficiencies, incisional hernia and weight loss. We report a case of unexplained adrenal insufficiency in a patient who had gastric bypass surgery.

Case

A 77-year-old gentleman presented with a history of recurrent hypoglycaemic episodes. Hypoglycaemic symptoms occurred on a daily basis over several years with capillary blood glucose readings ranging between 1.9 and 2.5 mmol/l during episodes. He was diagnosed with dumping syndrome following gastric bypass surgery 18 years when pyloroplasty and vagotomy had not worked for severe reflux oesophagitis. He had significant weight loss following that surgery. There was no history of diabetes or ingestion of any medication that could cause hypoglycaemia. He was taking adequate nutrition.

Investigations and Management

His random cortisol was 26 nmol/l and a subsequent Short Synacthen test showed an inadequate response (0-min cortisol of 25 nmol/l and 30-min cortisol of 156 nmol/l), adrenal antibodies were negative and serum adrenocorticotrophic hormone (ACTH) level was less than 5, indicating adrenal hypofunction secondary to ACTH failure. Other pituitary hormones and blood results (thyroid, liver, renal function) were normal. Pituitary MRI and adrenal CT were normal. He was commenced on hydrocortisone 20 mg a day and the frequency of hypoglycaemic episodes went down from once a day to once a month.

Discussion

The cause of adrenal insufficiency in this case remains unexplained. Possible mechanisms include malabsorption of bile, trace elements and essential vitamins resulting in reduced steroid synthesis, weight-loss-related re-setting of hypothalamo–pituitary–adrenal axis following drastic weight loss, and perio-perative complication from blood loss resulting in pituitary apoplexy. This case emphasises the importance of endocrine surveillance as part of the long-term follow-up for patients after excessive weight loss post gastric surgery.

DOI: 10.1530/endoabs.65.P55

P56

A case of anaphylaxis in phaeochromocytoma

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Introduction

The physiological actions of catecholamines have led to the empirical use of adrenaline in the management of anaphylaxis, with alpha-adrenergic activation increasing peripheral vascular resistance and beta-adrenergic activation relaxing bronchial smooth muscle and inhibiting histamine release. Supraphysiological levels of catecholamines are released by phaeochromocytoma and hence blockade of these same receptors is required for symptom control, prevention of end organ damage and to facilitate safer operative management. The management of a severe allergic reaction in the setting of phaeochromocytoma is an unknown entity.

Case

56 year old female with an incidental adrenal adenoma with mild hypertension (mean daytime BP 151/99) was investigated. Investigations showed raised urine metanephrines- 9538 *units* (Upper Limit 4400 *units*), and single photon emission CT confirmed bilateral phaeochromocytoma. Subsequently she was managed medically as per local guidelines, titrating up to 8 mg Doxazosin three times daily and *25* mg Atenolol twice daily prior to bilateral adrenalectomy, without the use of phenoxybenzamine. During anaesthetic induction the patient suddenly felt her throat swelling and developed difficulty with breathing. Her blood pressure dropped to 76/45 and she became tachycardic. A diagnosis of a severe anaphylactic reaction to an unknown agent was made. She recovered quickly following rapid introduction of Intravenous hydrocortisone and anti-histamines given by the adrenal anaesthetist and inotropic intervention. Later Immunological testing confirmed an unknown severe allergy to penicillin.

Conclusion

Anaphylaxis in patients with phaeochromocytoma can occur despite supraphysio-logical levels of catecholamines. Possible reasons for this are the down regulation of adrenergic receptors due to chronic exposure to catecholamines, and the effect of optimised alpha blockade, leading to severe anaphylaxis upon exposure to a trigger. The use of the competitive alpha blocker doxazosin instead of the non-competitive alpha blocker phenoxybenzamine, whilst still debated, probably contributed to the patient's rapid response to inotropes which saved her life.

DOI: 10.1530/endoabs.65.P56

P57

A case of familial hyperkalemia due to Gordon's syndrome

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Gordon's syndrome is a rare, autosomal dominant disorder characterized by hyperkalaemia, hypertension, mild hyperchloraemic metabolic acidosis despite normal glomerular filtration rate, with low or low-normal plasma renin activity and aldosterone concentrations. Here we describe a case of Gordon's syndrome presenting a diagnostic challenge. She first presented age 17 yrs with constipation and abdominal pain. No significant past medical or medication history to note. General examination was unremarkable. BP126/60. She was incidentally noted to have raised potassium: 7.1 mmol/l with normal renal function. 24 h urine potassium, urinary catecholamine's, Serum aldosterone, renin, fasting blood glucose, short synacthen test and autoimmune profile were normal. A presumptive diagnosis of Isolated Hypoaldosteronism versus Renal Tubular Acidosis was made and fludrocortisone therapy was started. She refused genetic testing. Age 20, she was readmitted with hyperkalaemia and elevated BP170/100. Secondary causes of hypertension excluded and fludrocortisone dose reduced. During follow up , we kept open mind regarding underlying cause for Hyperkalemia. As she was asymptomatic, she refused genetic testing and did not undertake all investigations as suggested. Finally age 29 years, she agreed genetic testing which confirmed Gordon's syndrome (*pseudohypoaldosteronism* type II). Fludrocortisone was stopped, thiazide diuretic started with good results and no further episodes of hyperkalemia. Thiazides are known to correct chloride dependent clinical features in this condition. Since above diagnosis, her mother, sister and her son have been tested positive for Gorden Syndrome. Even though Gordon's syndrome, is characterized by salt-dependent hypertension, *hyperkalemia* and *metabolic acidosis*, our patient only had isolated hyperkalemia. A high index of suspicion is required to diagnose this condition. Although genetic link was suspected for several years, it took almost 12 years to finally achieve a correct diagnosis and initiating appropriate management.

DOI: 10.1530/endoabs.65.P57

P58

Safe withdrawal of corticosteroids after prolonged use: a call for a national protocol

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Introduction
Prolonged therapy with high-dose corticosteroids ($\geq$ 7.5 mg Prednisolone or 1–1.5 mg Dexamethasone daily) can result in adrenal atrophy and hypofunction. Abrupt withdrawal of corticosteroids after prolonged use can lead to adrenal insufficiency, corticosteroid withdrawal symptoms or a relapse of the initial disease. There are several in-house protocols for safe corticosteroid dose tapering but a national protocol is required.
Our protocol
Patients are informed of the problems that may be encountered during corticosteroid withdrawal after short-term, intermediate-term and long-term use: namely symptoms of adrenal insufficiency, corticosteroid-withdrawal or relapse of the initial disease for which the corticosteroid was started. Recovery of the adrenal gland function can be very slow if there is going to be any recovery at all. High doses of corticosteroids can be rapidly reduced over 1–4 weeks to a Prednisolone equivalent of 7.5 mg daily depending on symptoms. Some physicians may convert to Hydrocortisone at this stage. Otherwise we reduce the Prednisolone dose by 0.5 mg every month depending on symptoms. Once the patient is on 3–3.5 mg daily we arrange a Short Synacthen test to assess adrenal gland function on a morning before Prednisolone ingestion. This can also be done after a weekend conversion to Hydrocortisone. If adrenal gland function is normal we stop or continue to tail down the Prednisolone dose according to symptoms. If adrenal function is still subnormal the patient can stay on the same dose or a higher dose depending on symptoms. A repeat Short Synacthen test after 2–3 months will help decide if patient should stay on lifelong physiological-dose corticosteroid replacement.
Conclusion
Our protocol ensures the provision of adequate information to the patient concerning the problems of corticosteroid withdrawal after prolonged use, a safe and flexible corticosteroid withdrawal regimen, and ensures regular adrenal function assessment during and after successful corticosteroid withdrawal.

DOI: 10.1530/endoabs.65.P58

P59

Real life experience of 8 people with adrenal insufficiency using subcutaneous hydrocortisone infusion in continuous and pulsatile regimens recruited through hydrocortisone pump support group

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Subcutaneous hydrocortisone (HC) infusion using continuous (CSHI) and pulsatile (PSHI) regimes are treatment options for adrenal insufficiency. It is an off-labelled treatment in UK for patients with adrenal insufficiency (AI). We surveyed 8 cohorts via Cortisol Pump UK support group in Facebook to capture their data in the following area:

- Quality of Life AddiQoL scores
- 24 h infusion doses & type of regimens
- HC doses according to body surface area (BSA)
- A&E, hospital admission before & after starting on HC pump Improvement since started on HC pump
- Challenges with HC pump.

Results
Mean age 47 (31–51); 8F; Mean AddiQoL score 87.5/120 2 primary AI, 2 unknown, 4 secondary AI. 6 on CSHI, 2 on PSHI Mean length of time on infusion 12 months (10 days–22 months); mean body surface area dose per day 17.425 m
Conclusions
Those with daily dose below 25 mg has a higher mean AddiQoL score compare to those with a daily dose above 30 mg (100/120 vs. 80/120). Mean daily rate per body surface area is higher than previous studies. A&E visits and hospital admissions in this cohort has reduced from 38 visits to 2 visits for the first 6 months or since started on pump. Larger studies are needed to look of the effects of these 2 regimens.

DOI: 10.1530/endoabs.65.P59

P60

Transient diabetes insipidus following aortic valve replacement

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Background
Postoperative diabetes insipidus (DI) occurs predominantly following pituitary surgery. Here we present a case of transient DI developing after coronary artery bypass surgery (CABG) and aortic valve replacement and discuss the potential mechanisms.
Case Presentation
A 69-year-old female with a past medical history of atrial fibrillation, hypertension and stroke was admitted for elective aortic valve replacement for severe aortic stenosis. The surgery was uneventful, but she developed thirst and polyuria (hourly urine output (UO) between 300 and 500 ml/h) on day 1 postoperatively. This was initially managed with matched input/output balance. The serum sodium remained normal (142 mmol/l) and serum osmolality at the time was 290 mOSm/kg. DI was suspected; this was supported by a low urine specific gravity reading. However, the polyuria failed to settle hence a single dose of 1mg subcutaneous desmopressin was given. Her symptoms subsequently improved with UO of 50–90 ml/hr the following day. MRI pituitary was unremarkable. At day 4 the UO again increased (up to 350 mls/hr), requiring a second dose of subcutaneous desmopressin. Her symptoms subsequently settled.
Discussion
Postoperative polyuria following cardiac surgery should alert clinicians towards a possible diagnosis of transient DI. The mechanism behind this rare phenomenon is not clear. The cardiac standstill during extracorporeal circulation most probably affects the function of nonosmotic receptors located in the left atrium. This subsequently leads to suppression of ADH release. Additionally, volume loading during such procedures leads to myocyte rigidity and increase in natriuretic peptide secretion which contributes to the polyuria. DI post cardiac surgery is transient and responds to desmopressin replacement. Our case is the only one reported in adults where more than one dose of desmopressin was required.

DOI: 10.1530/endoabs.65.P60

P61

Retrospective audit of adrenal incidentaloma

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Background
The incidental adrenal lesion, coined *'incidentaloma'*, is a common radiological finding, necessary of further investigation and diagnosis
Aims
This is a retrospective observational study which aims to identify the prevalence of incidentaloma in CT scans of the abdomen and pelvis in the Brighton & Sussex University Hospital's Trust. Our additional objective is to assess the adequacy of incidentaloma management through adherence to current guidelines.
Materials and methods
1169 CT scans involving the abdomen and pelvis were reviewed for the presence of adrenal incidentaloma between 1 January 2015 and 31 January 2015. Patients identified to have an incidentaloma then had their clinical records reviewed.
Results
Only 28.14% of all radiologist reports reviewed contained a comment on adrenal appearance and 39 individuals (3.34%) were found to have an incidentaloma. Excluding patients who had since passed away, had cancer of another organ or were otherwise too frail, 4 of a possible 15 (26.67%) were followed up in some capacity. 20% were reviewed in clinic, 20% were assessed for hypercortisolism and 20% were assessed for pheochromocytoma.
Conclusion
The prevalence of adrenal incidentaloma is statistically similar to audits of a similar nature. However, management of incidentaloma in the trust shows poor adherence to existing clinical practise guidelines as not all incidentaloma patients were referred to the endocrinology department. We therefore recommend improved consistency in radiologist reports on the adrenals through the implementation of adrenal 'autotext' and to ensure trust doctors are aware that every incidentaloma is necessary of endocrine referral.

DOI: 10.1530/endoabs.65.P61

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A service evaluation for patients with adrenal incidentalomas

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Introduction
Adrenal incidentalomas are increasingly found in patients imaged for investigation. A service evaluation was undertaken to standardise care for these patients in line with the European Society of Endocrinology Guidelines.
Aim
Standardise the care for patients with adrenal adenomas at Royal Liverpool University Hospital.
Method
Retrospective review of 70 patients with adrenal incidentalomas over 2 years (January 2016–December 2018).
Results
70 patients with 86 adrenal adenomas (16 bilateral) were included. 87% were found incidentally, 6% had adrenal specific symptoms and 7% were known to have adenomas already. The associated comorbidities were hypertension (57%), cardiovascular disease (36%), diabetes (21%) and osteoporosis (4%). 21% had no comorbidities. 69% were picked up on CT and 31% on MRI. There was consistency in MRI reporting with 89% referencing signal dropout on reports but only 25% CT reports had specific hounsfield units. 42% of the lesions were <2 cm, 51% 2–4 cm and 7% >4 cm. 91% were reported as benign, 7% indeterminate and 2% as heterogeneous requiring surgery but were benign on histology post-surgery. Cortisol, aldosterone and metadrenalines hormones were assessed in; 90%, 87% and 89% respectively and sex hormones in 44% of the patients as this were only checked in females appropriately. 43% patients were initially referred to endocrine surgery, 37% to endocrinology, 11% were under both specialities and 9% patients were not referred to either. 61% of the patients were still being followed up. 20% for inconclusive biochemical findings, 11% for inconclusive radiology, and 5% awaiting investigations. 25% were followed up despite the adenomas being reported as benign and hormonal screening being negative.
Conclusion
To avoid overinvestigation and medicalization of patients, and for best use of resources, a streamlined audited pathway is necessary as cases originate in a wide variety of departments.

DOI: 10.1530/endoabs.65.P62

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Adrenal medullary hyperplasia mimicking phaeochromocytoma – a case report

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Introduction
Adrenal medullary hyperplasia (AMH) is a rare syndrome of catecholamine excess.
Case
A 59 year old lady known to suffer from hypertension underwent a computed tomography scan of the abdomen as further investigation for unprovoked deep vein thrombosis. This showed a 37 mm right adrenal mass which enhancedheterogeneously with contrast on the porto-venous phase and became homogenously hyperdense on the delayed phase. Findings were not typical of an adrenal adenoma. The patient was asymptomatic and denied headaches, sweating, palpitations or postural symptoms. Baseline investigations for an adrenal mass including urinary freecortisol, adrenal androgens, aldosterone renin ratio and Chromogranin A were normal. However, she had persistently raised serum noradrenaline levels up to 1120 ng/l (upper limit 420 ng/l). MIBG scan did not show any evidence of phaeochromocytoma and PET CT was negative. MR adrenals confirmed the presence of 2.2×3.3 cm mass but unfortunately, there were no definite features to suggest a specific entity for the cause of the adrenal mass. Thus, the patient underwent right laparoscopic adrenalectomy with adequate pre-operative alpha blockade. Histology confirmed AMH. The adrenal medulla did not exceed 8 mm in size. It stained for Chromogranin A and Synaptophysin. HMB45, S-100 and Ki-67 were negative. The adrenal cortex was unremarkable. Our patient remains clinically well.
Conclusion
AMH is a begin nodular and/or diffuse lesion of the adrenal medulla that is less than 1 cm in maximum diameter. It consists of an increase in the number of chromaffin cells in the adrenal medulla. Lesions larger than 1cm are classified as phaeochromocytomas. AMH can only be diagnosed histologically. AMH is a recognized precursor for phaeochromocytoma in MEN 2 but not in isolated cases. Most AMH cases are picked up during surveillance in patients known to have hereditary PCC. Sporadic AMH is an extremely rare entity.

DOI: 10.1530/endoabs.65.P63

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Primary aldosteronism (PA) – clinical and hormonal characteristics of a series of patients

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Background
PA is a frequent cause (5–13%) of secondary hypertension (HT), yet diagnostic work-up of PA remains challenging.
Aim
To describe the characteristics of hypertensive patients diagnosed with PA, biochemical screening (aldosterone:renin ratio/ARR), confirmatory tests, and adrenal CT results.
Methods
Clinical, hormonal and imaging evaluation.
Results
13 patients (7M/6F) with PA were 45 yrs (40–50) old at presentation (median/range). Ten patients (76.9%) had stage 3 and three had stage 2 HT. Systolic BP was 150 mmHg (140–167.5), diastolic BP 100 mmHg (80–110). Patients took 2 (2–4) classes of antihypertensives and HT duration was 10 yrs (0–15). Seven patients (53.8%) presented hypokaliemia history, while 2 associated sleep apneea. ARR on RAAS-interfering drugs (ARRon) was 72.6 (42.9–164.9), serum potassium was 4.18 mmol/l (3.5–4.5); one patient associated unsuppressed cortisolemia $=6.39$ mc g/dl after 1 mg overnight dexamethasone. Repeated ARR after RAAS-interfering drugs discontinuation in 9 patients (ARRoff) was 82.35 (32.9–626.7). We performed 15 confirmatory tests in 12 patients: 10 saline infusion tests (SIT), 4 captopril challenge tests (CCT) and one oral salt loading. Nine patients were SIT-positive (aldosterone> 5ng/dl), 2 patients were CCT-positive (aldosterone supression $<30\%$), one CCT-negative patient (2h suppression $=25.6\%$) was SIT-positive. SIT-positive patients had higher ARRon than CCT-positive patients (82.8 vs. 45.93). Adrenal CT identified unilateral adenomas in 8 patients (61.5%), 3 of whom associated a diffusely enlarged contralateral adrenal. One patient was biochemically cured after unilateral adrenalectomy, the remaining 12 received mineralocorticoid receptor antagonists. After 2.4 years (0.75–3.05) follow-up, 8 patients were controlled (BP $<140/90$ mmHg). Target organ complications were present in 10 (76.9%) patients: 8 presented cardiomiopathy, 8 had CKD and 3 patients had retinopathy.
Conclusions
PA was a frequent cause of severe secondary HT in our cohort. ARR was lower in patients taking RAAS-interfering medication. SIT-positivity associated with higher ARR than CCT-positivity. Unilateral adrenal nodules were more prevalent than idiopathic PA in our patients.

DOI: 10.1530/endoabs.65.P64

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Maturity onset diabetes of the young: a first case description of PAX4 mutation in the UAE

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Introduction
Maturity-onset diabetes of the young (MODY) is a genetically and clinically heterogeneous type of diabetes mellitus, characterized by early onset (often before 25 years of age) and absence of pancreatic autoimmunity markers.
Case
We report a 20 years old female diagnosed with type 1 diabetes at age 18, with positive glutamic acid decarboxylase antibodies and low C peptide level. She had

no history of diabetic ketoacidosis or hypoglycemia. Her parents did not have Diabetes, however her mother had a history of gestational diabetes. Insulin treatment was started at age of 18 (only Glargine), she was taking insulin for 3 months and her hyperglycemia improved then she stopped insulin by her own for more than a month. No Osmatic symptoms or no DKA episode happened after omission of her insulin, her home blood glucose levels were oscillating between 200 and 400 mg/dl. Her HbA1c ranged from 8 to 10% without being on any form of insulin or oral hypoglycemic agent. Then, a blood test was sent for genetic screening of monogenic diabetes, and turn out positive for MODY (**Heterozygous in the *PAX4* gene**). Afterwards she was commenced on glimepiride 2 mg her blood glucose subsequently improved. 3 months later her HbA1c impressively improved to 6.6%.

Conclusion

We present a case of PAX4 gene mutation with an early-onset diabetes mellitus, manifests as transcription factor which is a member of PAX family located on chromosome 7 and regulates fetal development, also represses th PAX4 is required for the regeneration of β-cells in adults and its mutation blocks or inhibits β-cell proliferation. Two PAX4 gene mutations were reported as the cause of monogenetic form of diabetes in Thai population termed MODY 9. To our knowledge, the present case demonstrates that a novel mutation of *PAX4* is likely to be associated with diabetes and it is the first case to be reported in the Middle East and United Arab Emiratis.

DOI: 10.1530/endoabs.65.P65

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Waterhouse–Friderichsen syndrome: an endocrine emergency

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Waterhouse–Friderichsen Syndrome is adrenal gland failure due to adrenal haemorrhage. It is an uncommon but usually life-threatening condition, which can be one of the serious complications of severe sepsis. Clinical manifestations of adrenal haemorrhage can vary widely depending on the degree and rate of haemorrhage. Adrenal haemorrhage may result from trauma, sepsis, anticoagulation medication, coagulopathy, autoimmune conditions, underlying tumour or idiopathic disease. We present a case of Waterhouse–Friderichsen syndrome in a 45-year-old female with no significant past medical history apart from hypertension, who was admitted for sepsis with pyrexia, extreme lethargy, recent UTI and diarrhoea and digital finger ischaemia, complicated by sudden onset refractory shock and disseminated intravascular coagulopathy. There was a note of digital splinter haemorrhages with no generalised rash. There was no evidence of infective endocarditis on echocardiogram. CT abdomen showed inflammatory colitis with mesenteric lymphadenopathy and bilateral non traumatic adrenal haematomas. All microbiological cultures and viral serology were negative. She was immediately treated with intravenous antibiotics and steroids and subsequently made good recovery. Patient was discharged with replacement hydrocortisone and fludrocortisone and followed up in the endocrine clinic. In view of digital ischaemia, left calf skin ulcer and mononeuritis multiplex, she was reviewed by Rheumatology and Dermatology and managed as antiphospholipid syndrome with vasculitis. Her skin biopsy result of left calf ulcer showed dermal ulcer with occlusive thrombi and she was initiated on warfarin and prednisolone.

Conclusion

In the medical emergency setting, it is important to consider the diagnosis of Waterhouse–Friderichsen Syndrome, based on the clinical features of adrenal insufficiency (refractory shock) in a septic patient. This case highlights the value of prompt recognition and rapid steroid replacement, which are lifesaving. Finally, investigations for the underlying aetiology of adrenal haemorrhage, such as sepsis and autoimmune condition, should be undertaken.

DOI: 10.1530/endoabs.65.P66

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New onset paranoid psychosis associated with 'incidental' pheochromocytoma

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We present a case of 70 year-old-man, who was referred to the endocrine clinic with incidentally detected 26 mm lesion arising from the left adrenal gland suspicious of pheochromocytoma. This was detected during investigations for asymptomatic microscopic haematuria. He did not describe the typical symptoms of pheochromocytoma (episodic headaches, sweating, tachycardia), but interestingly 4–5 months previously was diagnosed with an acute onset of psychosis with paranoid delusions from completely normal mental state and commenced Quetiapine and Mirtazapine. On direct focused questioning regarding any episodic symptoms, he described episodic attacks of anxiety associated with flushing and palpitations, sometimes nocturnal. He was noted to be hypertensive in clinic (170/80). His biochemistry confirmed elevated urine normetanephrine (14.18 umol/24 h, ref: 0.00–3.00 umol/24 h), mildly raised urine 3-methoxytyramine (3.24 umol/24 h, ref: 0.57–2.39 umol/24 h) and significantly raised plasma normetanephrine (4526.9 pmol/l, ref: 0–1180 pmol/l). Following preparation with phenoxybenzamine, he underwent laparoscopic adrenalectomy resulting in complete normalisation of hypertension. Histology confirmed pheochromocytoma. Post-operative period was complicated with transient delirium, which fully resolved. Few months post adrenalectomy he reported significant improvement in his mood and anxiety. His medications were changed from Quetiapine to Risperidone due to dizziness. Although he remains on Risperidone, his mental health is much more stable, and he is now being described as back to his usual self by his family and his psychiatrist.

Discussion

Several cases of pheochromocytoma presenting with psychosis were described in literature. Various theories have been proposed to explain this possible association-dopamine theory or theory of unidentified antibody associated with pheochromocytoma potentially causing a picture similar to paraneoplastic encephalitis. Although our patient continued antipsychotic medication post operatively, his condition became much more stable and easier to control. Similarly, to thyroid tests, screening for pheochromocytoma should perhaps be considered in patients presenting with a new diagnosis of acute psychosis.

DOI: 10.1530/endoabs.65.P67

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Unusual case of aldosterone and cortisol co-secreting adrenal adenoma

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72 year old female presented with lower abdominal pain and was incidentally noted to have right adrenal adenoma. On further evaluation, she was noted to be experiencing excessive weight gain despite healthy lifestyle, low trauma fracture right wrist 3 yrs ago and uncontrolled hypertension despite taking 3 anti-hypertensive medications. She had no overt clinical features of Cushing's such as striae, proximal myopathy, thinning of skin or easy bruising. Screening biochemistry revealed raised aldosterone:renin ratio. Subsequent saline suppression test confirmed diagnosis of primary hyperaldosteronism. In addition, endocrine testing confirmed excessive cortisol production (abnormal overnight dexamethasone suppression test, 24 h urine cortisol × 2 and a low dose dexamethasone suppression test). Following discussion in adrenal MDT, she underwent right adrenalectomy. She was started on hydrocortisone replacement postoperatively due to concerns of developing adrenal insufficiency secondary to suppression of hypothalamic–pituitary–adrenal axis following removal of a tumor that secretes glucocorticoids. A well circumscribed, homogenous and bright golden yellow adrenal adenoma without evidence of malignancy was confirmed histopathologically. Six weeks post-adrenalectomy, repeat testing showed equivocal aldosterone:renin ratio. During postoperative period, she had adequate cortisol response to short synachthen test hence she was gradually weaned off hydrocortisone replacement therapy. Six months postoperatively her Aldosterone : rennin ratio and 24 h urine cortisol measurements done twice are within normal reference range. At present, her BP is controlled on single antihypertensive agent (Doxazosin 4 mg).

Conclusion

It is important to recognize co-secreting adrenal adenomas. Given that most cases are unilateral, postoperative adrenal crisis or symptomatic adrenal insufficiency can occur in patients who had undiagnosed or untreated adrenal adenomas co-secreting excess mineralocorticoids and glucocorticoids. In addition, these patients require regular monitoring as incidence of cardiovascular and metabolic disorders in Aldosterone- and cortisol-coproducing adrenal adenoma is significantly higher than that of the pure aldosterone producing adenoma.

DOI: 10.1530/endoabs.65.P68

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Adrenal incidentaloma multi-disciplinary investigation and management at University Hospitals of Derby and Burton Foundation Trust

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Introduction
Incidental indeterminate adrenal nodules discovered on imaging in patients under the care of University Hospitals of Derby and Burton Foundation Trust are discussed in Urology MDT. MDT cases were reviewed for a 12 month period before an endocrinologist joined the MDT in January 2018 and 12 months afterwards, to review the compliance of local practice with European Society of Endocrinology (ESE) Guidelines for the management of adrenal incidentalomas.
Results
45 patients had adrenal nodules (12–160 mm in maximum diameter) discovered on abdominal imaging; CT ($n=41$), MRI ($n=2$), MRCP ($n=1$), CTA ($n=1$), with HU >10 in 84% of cases ($n=38$). 39 patients had a unilateral nodule (Right $n=14$, Left $n=25$) with bilateral adrenal nodules in 6 patients. Adrenal nodule was associated with malignancy in 27% ($n=12$) of these patients, with metastatic disease diagnosed from primary lung ($n=3$), RCC ($n=1$) and DLCBC Lymphoma ($n=1$) as well as primary adrenal malignancy; sarcoma ($n=1$) and adrenocortical carcinoma ($n=1$). Investigation of hormone excess was carried out (Table 1). Non-functioning incidentaloma were diagnosed ($n=21$), the most common active nodule found was Phaeochromocytoma ($n=6$), Aldosterone secreting ($n=2$) and Cortisol secreting ($n=1$). 27% ($n=12$) of patients were scheduled for, or had undergone adrenalectomy.

Table 1

Differential Diagnosis	Assessment	2017 (%)	2018 (%)
Clinical evidence of hormone excess	Outpatient Clinic review by endocrinologist	6 (29)	19 (79)
Phaeochromocytoma	Plasma or Urine Metadrenalines	12 (57)	18 (75)
Cushings	9AM ACTH, Overnight Dexamethasone Suppression or 24 hr Urine Cortisol	5 (24)	15 (63)
Adrenocortical Carcinoma	Steroid precursors-DHEAS, 17-OHP	3 (14)	11 (46)
Conns	Renin and Aldosterone	5 (24)	10 (42)

Conclusion
Local review of adrenal incidentaloma cases, following introduction of an Endocrinologist to MDT, argues for an improved and comprehensive assessment with particular reference to functional lesions. Implementation of a structured local guideline, may improve ESE adherence, to optimise management of functional adrenal incidentalomas.

DOI: 10.1530/endoabs.65.P69

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Comparison of adrenal incidentalomas management in single Trust with reference of European society of endocrinology guidelines

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Aim
This audit aims to access the compliance in management of adrenal incidentalomas with reference of European society of endocrinology guidelines.
Background
An adrenal incidentaloma is a mass lesion greater than 1 cm in diameter, serendipitously discovered on radiological examination. It is important to determine its malignant potential and functional status. European society of Endocrinology (ESE) has published its guidelines in 2016 for management of adrenal incidentalomas.
Methods
Patients with known adrenal incidentalomas were collected from Adrenal multidisciplinary team (MDT) meeting from October 2017 to February 2018. There were total 56 patients with 32 females and 24 males. As per ESE guidelines every patient should be evaluated for cortisol and catecholamines excess with overnight dexamethasone suppression test (ONDST) and urinary or plasma metanephrines. Aldosterone renin ratio (ARR) should only be performed in patients with known history of hypertension (HTN).
Results
ONDST and plasma/urinary metanephrines were not performed in 12 (21%) and 5 (8%) of patients respectively. Whereas Aldosterone renin ratio (ARR) was checked in 20 (35%) patients with no history of Hypertension (HTN).
Conclusion
This study demonstrates that ESE guidelines were largely followed but there is still need for better compliance.

DOI: 10.1530/endoabs.65.P70

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Autonomous cortisol secretion in adrenal incidentalomas

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Introduction
Adrenal incidentalomas are common occurrence with up to 3–10% of the general population who have imaging. Up to 20% of them may have autonomous cortisol secretion (ACS), a term that refers to biochemical evidence of excess cortisol, but without the overt cushing's syndrome.
Aim
Prevalence of ACS in our cohort of patients with adrenal incidentalomas and review their care.
Method
Retrospective review of 70 patients with adrenal incidentalomas over 2 years (January 2016–December 2018)
Results
70 patients with adrenal adenomas of which 16 patients had bilateral lesions (86 adrenal adenomas) were included. 90% of them had hormone assessment for cortisol and 24% of them had 24 h urinary free cortisol with rest of them underwent 1 mg overnight dexamethasone suppression test. 19% had levels in the range for ACS. None of them had overt cushing's syndrome. Only 16% of them had cushing's specific symptoms, reported easy bruising. Of the comorbidities, 75% of them hypertension, 33% type 2 diabetes, 33% had bone mineral density in the range of osteopenia/osteoporosis, and 25% had cardiovascular complications. 58% of them had single and 42% of them had bilateral adrenal lesions. Of the 17 lesions individually analysed, most (65%) were in the 2–4 cm range, followed by lesions less than 2 cm (24%) and least common were lesions more than 4 cm (11%). 58% of them were appropriately being followed up by endocrinology team but 42% of them followed up elsewhere.
Conclusion
The prevalence of ACS in our patient cohort with adrenal incidentalomas was similar to previously published reports i.e. up to one fifth. Nearly one third of the patients who had bilateral adrenal incidentalomas had ACS. This emphasizes the need for careful clinical and biochemical assessment for adrenal hormone excess by endocrinology team in people with adrenal incidentalomas.

DOI: 10.1530/endoabs.65.P71

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Management of adrenal incidentaloma: a DGH experience

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Incidental adrenal masses is a common finding on abdominal imaging completed for other reasons. Majority of these masses are benign non-functioning adenomas. Investigations are required to ensure they are benign and do not have autonomous hormonal secretion.
Aim
We completed an audit to review current practice in the assessment of adrenal incidentaloma at our organisation, a mid-size acute DGH, and compared it with

European Society of Endocrinology (ESE) Clinical Practice Guideline 2016, on management of adrenal incidentalomas.
Methods
A search of CT and MRI report database with the key words 'adrenal adenoma' and 'adrenal mass' from January 2014 to December 2015 was used to identify patients. Patients with previous adrenal history were excluded. Relevant clinical data was identified by reviewing electronic patient records. A total of 231 patients were included in our audit.
Results
2/3rd of the imaging reports described features consistent with benign adenomas. 26% of cases were further investigated with repeat imaging and only 18% of cases had hormonal testing completed.
Discussion
The purpose of further evaluation of incidental adrenal findings is to exclude any functionally active or malignant tumours. Our results show that a large proportion of patients with adrenal incidentalomas did not have investigations to exclude autonomous hormonal secretion as recommended by the ESE guidelines, and a quarter of patients had repeat imaging despite benign appearances on initial imaging. This audit identified the need to develop a local policy for investigating incidental adrenal findings by non-specialists and setting up a dedicated MDT service to streamline further investigations and management.

DOI: 10.1530/endoabs.65.P72

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Heparin-induced hypo-aldosteronism and hyperkalemia

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We present an interesting case of Heparin induced hypoaldosteronism associated hyperkalemia in a 69 year old man with a prosthetic heart valve requiring a right sided nephrectomy for a liposarcoma. His persistent hyperkalaemia failed to respond to conventional treatment initially but a switch to Warfarin and use of oral Fludrocortisone was effective in normalisation of observed high renin and low aldosterone levels. Early and timely recognition of Heparin induced hypoaldosteronism associated hyperkalemia remains a challenge especially in busy acute care settings. Heparin induced hyperkalaemia can be a life-threatening emergency. Early recognition of hyperkalaemia can improve patients' outcomes. We present a case which highlights the importance of assessing risk benefit ratio at time of initiating heparin therapy which can be associated with persistent hyperkalemia due to underlying hypoaldosteronism. We present a man in his sixties with a past medical history of type 2 diabetes mellitus (T2DM) and mechanical aortic valve prosthesis requiring regular anti coagulation with Warfarin. He presented with a large abdominal mass and his CAT imaging revealed an underlying retro peritoneal tumour which was later confirmed on further histology. His diabetes medications included Metformin and Gliclazide. His Warfarin was discontinued pre operatively and Tinzapirin was commenced post-surgery but had to be discontinued due to hemi-peritoneum and bowel perforation. It was observed that his serum K was elevated on day 5 post LMWH initiation. His ECG showed no hyperkalaemic changes. From above discussion, we advocate that high degree of suspicion needs to be exercised for potentially life-threatening and reversible condition like hyperkalaemia. Clinicians should be aware that hyperkalaemia could be caused by LMWH especially in multi-morbid surgical patients, where bleeding and thrombotic risks need to be assessed. A multi disciplinary approach is necessary for optimal therapy but further randomised controlled trial data is required to develop future guidelines.

DOI: 10.1530/endoabs.65.P73

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Symptomatic hyponatraemia due to valerian extract use

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A middle aged woman was admitted to Salisbury District Hospital after she was found to be severely hyponatraemic by her GP. She had been suffering from lightheadedness, headaches and tiredness for a few weeks before her admission but there was no obvious aetiology. Her past medical history included hypertension but she was not on diuretics or any other medication that could affect her sodium levels. Her serum sodium at the GP surgery was 123 and when she was admitted in the Acute Medical Unit in Salisbury District Hospital it was 122. Her baseline serum sodium levels were between 132 and 134 in the past. Her clinical examination was normal. There was no evidence of fluid overload or dehydration. She was diagnosed with symptomatic euvolaemic hyponatraemia. She had never had hyponatraemia in the past. There was no history of smoking, excess alcohol consumption or excessive oral fluid consumption. The patient did mention she had started taking an over the counter drug to reduce her anxiety and improve her sleep. That substance included valerian extract (KALMS, https://www.kalmsrange.com/kalms-range/). She was using it regularly during the day 3–4 times. Her creatinine, urea and eGFR were normal. The rest of the electrolytes, the thyroid function tests and the cortisol levels were also normal. Her serum osmolality was low, her urine osmolality was high and the urine sodium level was 21. She was managed with oral sodium tablets, fluid restriction up to 1.5 l per day and monitoring of her sodium levels. She was advised to stop the valerian extract containing product. After 4 days of admission, her sodium levels normalised, her symptoms disappeared and she was discharged home. A week after her discharge her sodium levels remained normal after having being checked again at her GP Surgery.

DOI: 10.1530/endoabs.65.P74

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Review of the adrenal surgeries at East Sussex Hospitals Trust over 2 years

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Introduction
Prior to 2015 there was no pathway for adrenal masses. An Adrenal MDT was started to discuss all the adrenal nodules (except for suspected phaechromocytoma and adrenal carcinoma) to improve the service for this cohort of patients. This audit is a review of the impact of this intervention.
Methods
Data was collected between April 2016 and March 2016 for all adrenalectomies performed at East Sussex Hospitals Trust. Data was collected from the TheatreMan surgical database.
Results
27 patients had had Adrenalectomy surgery. 6 patients (22%) had adrenalectomy for functioning adrenal lesions: 2 with Conns syndrome, 1 patient with adrenal Cushings, 2 patients with Subclinical Cushing (probable autonomous cortisol secretion) and 1 patient has had combined aldosterone and steroid secreting lesion. Only 2 out of the 4 patients with adrenal cortisol secretion has had appropriate steroid cover during the perioperative period. 3 patients (11%) were found to have metastatic adrenal lesions and 18 patients (67%) had adrenalectomy as part of Radical nephrectomy for renal cell carcinoma.
Conclusion
We plan to introduce guidelines for steroid management for all steroid secreting adrenal tumours in perioperative period.

DOI: 10.1530/endoabs.65.P75

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Factitious Addison's disease in a young adolescent with type 1 diabetes

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Hypoglycaemia is a common side effect of insulin treatment in patients with type 1 diabetes mellitus (T1DM). A 16-year old girl with T1DM presented with a

recurrent hypoglycaemia, despite insulin dose reduction. Differential diagnosis included: overdose of insulin, Addison's disease, hyperthyroidism, insulinoma and anti-insulin antibodies. She was admitted to the hospital for observation and investigations. She had a low random cortisol level, leading us to start steroids and investigate her further for Addison's disease. Results of three short synachten tests were incongruous. During the admission, behavioural patterns were observed that suggested factitious causes. A psychiatrist saw her on several occasions. Initially, no concerns were raised. With a passage of time and follow up appointments, her father's behaviour indicated complex family dynamics that interfered with clinical picture. This case illustrates importance of a comprehensive approach to the investigation of hypoglycaemia with an emphasis on differential diagnoses, the dynamics of cortisol secretion and the effect of exogenous steroids on serum cortisol results interpretation. In a young adult's clinic, a psychologist is an essential team member dealing with all long-term conditions.

DOI: 10.1530/endoabs.65.P76

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Impacts and quality of life for people with adrenal insufficiency using Medical Detection Dogs before and after initiation of continuous subcutaneous hydrocortisone infusion (CSHI)

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Use of medical detection dog to improve hypoglycaemia awareness has been documented. However the data remain limited for people with adrenal insufficiency. We collected data retrospectively and prospectively on the episodes of low cortisol events initiated by medical detection dog and quality of life of 3 people with adrenal insufficiency before and started on continuous subcutaneous hydrocortisone infusion (CSHI) to correlate it with our Addison's Quality of Life scores. We also correlated the alert by Medical Detection Dog with cortisol blood tests for these cohort trying to capture the rise and fall cortisol while they are having their cortisol day curves. Conclusion is to be drawn to understand the role of Medical Detection Dog for people with adrenal insufficiency.

DOI: 10.1530/endoabs.65.P77

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The frustration of endocrine practice in a resource poor, developing country

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Background
The practice of endocrinology requires the support of good laboratory services in order to make accurate diagnosis of many endocrine disease. Many endocrine disorders appear rare in our country because of lack of reliable laboratory services. The following cases illustrate this frustration.
Case 1
A 39-year old caterer, known hypertensive but diagnosed diabetic recently when she developed a non-healing left foot ulcer and subsequent gangrene following a pedicure treatment 2 weeks earlier, for which she had an amputation. She had clinical features of Cushing's syndrome. Her urinary free cortisol was 965.2 (100–379) ug/day. Night (2300 h) serum cortisol was 249.59 (240–618) nmol/l while an overnight 1mg dexamethasone suppression test cortisol was 64.53 (240–618) nmol/l. Confusion came when we got another serum cortisol ('after dexamethasone') result that was neither requested for nor the sample sent) as 111.62 (<276 nmol/l)! This unsolicited result could not be satisfactorily explained by the lab, leaving us confused and frustrated as to the veracity of the results and how to proceed with the case.
Case 2
A 35-year old lady being managed for secondary adrenal insufficiency (and vitamin D deficiency) following prolonged use of steroids for suspected connective tissue disease. Her initial serum cortisol done a few days before her consultation with me was 1.47 (8.7–22.4) ug/dl. As she was symptomatic, she was started on 20 mg of hydrocortisone tablet while she repeated the serum cortisol for confirmation. The serum cortisol done 4 days after commencement of the hydrocortisone was reported to be 659 (171–536) nmol/l by another lab, that insisted after a doubt was raised that the rerun result was about the same (726.9). A recheck 2 days later at one of the initial labs showed 13.7 nmol/l. These inconsistent results were expensive and paid out-of-pocket by the patient.

DOI: 10.1530/endoabs.65.P78

Bone and Calcium

P79

Development of a long-acting parathyroid hormone for the treatment of hypoparathyroidism

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Background
Parathyroid hormone (PTH) is a peptide hormone consisting of 84 amino acids with residues 1–34 responsible for its biological activity. Hypoparathyroidism is a rare, complex condition with a patient predisposition toward impaired mineral homeostasis. Replacement with Natpara (PTH 1-84) requires daily injections and is still complicated by fluctuating calcium levels. An unmet need exists for a long-acting treatment that is effective. It is hypothesised that a PTH-Fusion with growth hormone binding protein (GHBP) will retain biological activity and have reduced renal clearance and proteolysis, thus prolonging the half-life of PTH.
Methods
Stable clones of two PTH fusions were generated: 14A8 (PTH fused to extracellular domain of PTH receptor and GHBP) and 14A7 (PTH fused to GHBP). Correct gene integration was confirmed by RT-PCR and sequencing. Proteins were expressed from suspension adapted CHO stable cell lines in roller bottle culture. 14A8 was purified by ion exchange and affinity chromatography. Potency assays were completed using a Dual Luciferase Reporter Assay (DLRA) and the PTH responsive cell line UMR-106.
Results
Sequencing confirmed gene integration and protein expression was confirmed by western blotting for both stable clones. 14A8 was purified to 2 mg/ml from roller bottle culture and shown to separate between 75 and 100 kDa by SDS–PAGE. Using the DLRA an EC_{50} for both PTH 1-34 and 14A8 were obtained: mean 54 vs. 1214 nM. 14A8 was ~22-fold less potent but had a higher maximal fold induction of 2.4-fold compared to PTH 1-34.
Conclusion
Fusions were successfully expressed from a stable CHO cell line and preliminary purification of 14A8 achieved. 14A8 exhibited a higher maximal fold induction, but was less potent than PTH 1-34. The reason for this is presently unknown but could be due to increased stability offered by the fusion, and will be further investigated.

DOI: 10.1530/endoabs.65.P79

P80

Assessing the use of Cinacalcet for conservative management of primary hyperparathyroidism in a regional district general hospital

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Background
The treatment of choice for symptomatic primary hyperparathyroidism (PHPT) is surgery, however in many cases patient choice or medical comorbidities preclude this treatment modality.
Aim
This audit examines the use of cinacalcet in management of primary hyperparathyroidism in a district general hospital to determine if it is in accordance with the National institute for health and care excellence (NICE) guidance (May 2019).
Method
We retrospectively analysed the data for all patients diagnosed with PHPT and treated with Cinacalcet in a district general hospital over a 12 month period.
Results
16 patients (10 female) were prescribed cinacalcet with an average age of 76. 100% of patients had calcium levels above 2.85 with symptoms or end organ damage, replete vitamin D levels and parathyroid hormone levels in keeping with PHPT. Urinary calcium:creatinine excretion ratio was appropriately screened to exclude familial hypocalciuric hypercalcaemia (FHH) in 14{87.5%} patients. 1{6.25%} patient was receiving cinacalcet for symptomatic FHH. 8{50%} patients were deemed unfit for surgery whilst 3{18.75%} are awaiting surgery. 2{12.5%} patients underwent unsuccessful surgery. 3/16{18.75%} patients refused Surgery. 10{62.5%} patients achieved a normalisation in calcium post cinacalcet treatment. 14{87.5%} patients had renal imaging with a total of 2{12.5%} having renal Calculi identified. In total 87.5% of cinacalcet prescriptions were compliant with NICE guidance. 16{100%} patients received a DEXA scan within 6 months of first clinic review
Conclusions
The study finds the majority of patients were able to achieve a normalisation in calcium following cinacalcet treatment. Predominantly cinacalcet was appropriately administered in accordance with NICE guidance. The results showed that cinacalcet had also been used as a bridging agent prior to definitive surgical intervention. This shows not all Cinacalcet prescriptions were compliant with NICE guidance but were deemed clinically necessary to prevent worsening hypercalcaemia.

DOI: 10.1530/endoabs.65.P80

P81

Relationships between serum calcium and parathyroid hormone levels on effectiveness of parathyroid scintigraphy with Sestamibi

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Introduction
99m/Tc-MIBI parathyroid scintigraphy (MIBI) is the most common test used for pre-operative localization of parathyroid adenoma in primary hyperparathyroidism. We evaluated the influence of serum calcium and parathyroid hormone (PTH) levels on sensitivity of MIBI imaging in successful parathyroid localisation in patients identified as having primary hyperparathyroidism.
Methods and material
Retrospective review of 403 patients who had MIBI scan as part of pre-operative assessment for localization of adenoma were included in this study. The relationships between serum calcium and PTH and sensitivity of MIBI were examined using the Student *t*-test for continuous variables and Chi-square test for categorical variables between the study groups. $P<0.05$ was considered significant.
Results
Of 403 patients, 279 (69.2%) were females and 124 (30.8%) were male. Mean age was 56 years (Range: 17–87). MIBI identified (positive scan) parathyroid adenoma in 260/403 (65%). The average corrected calcium concentration in patients with positive MIBI was 2.91 mmol/l (normal range 2.15–2.55 mmol/l); the value was 2.84 mmol/l in those with a negative MIBI scan ($P<0.01$). In this population none had a positive MIBI scan with serum calcium level <2.60 mmol/l. Similarly the average [PTH] in patients with a positive MIBI scan was 258 ng/l (normal range 10–65 ng/l), and 179 ng/l in those with a negative scan ($P=0.1$). The lowest [PTH] with a positive scan was 31 ng/l. Age and gender were not related to positivity of MIBI scan.
Conclusion
The likelihood of positive MIBI localisation increased with rising serum calcium but not PTH level. In 'mild' primary hyperparathyroidism with serum calcium <2.6 mmol/l MIBI did not identify an adenoma. We found that calcium is a better predictor of MIBI localisation than PTH. The performance of other imaging modalities (USS, PET, 4D CT) should be evaluated in 'mild' primary hyperparathyroidism.

DOI: 10.1530/endoabs.65.P81

P82

Association between lean mass and bone mass density in patients with inflammatory bowel disease

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Introduction
Patients with inflammatory bowel disease (IBD) are at increased risk for decreased bone mass density (BMD), fractures. Preserved muscle mass is important for healthy bones. Low mean mass can be found in these patients due to immobilization, lack of physical activity and glucocorticoids. Our aim was to evaluate the presence of low BMD and muscle mass impact on it.
Methods
64 patients with inflammatory bowel disease (40 with Crohn disease, 24 with ulcerative colitis, 35 women and 29 men, mean age 43.8 + 16.9 S.D., mean duration of the disease 9.1 + 7.1 S.D.), were evaluated between March 2018 and March 2019. We performed dual-energy X-ray absorptiometry for BMD-spine and femoral neck (FN) and whole-body scan. Muscle mass was estimated by with ASMI (ASM/height^2). Low BMD was defined according WHO as T score 2.5 S.D. in men aged >50 years and postmenopausal women, osteopenia between -1 and 2.49 S.D. and – score ≤ -2 S.D. below the expected range for gender and sex in the other patients.
Results
6 patients had fragility fracture, 2 young patients and 4 post-menopausal women. 4 had vertebral fractures, undiagnosed until the evaluation. According to the criteria mentioned above, low BMD was found in more than half of the patients (34/64 patients), osteoporosis in 9 patients, osteopenia in 12 patients, and BMD below the expected range in 13 patients. BMD was positively corelated with BMI ($P=0.03$). ASMI positively correlated with BMD both at the spine ($P<0.001$, $r=0.445$) and at the hip ($P=0.028$, $r=0.303$).
Conclusion
This study shows that, due to high frequency of bone abnormalities in patients with IBD, strategies to screen earlier in order to prevent fragility fractures should be elaborated. ASMI is an important predictor for BMD, underlining the importance of physical activity on preventing low BMD. Tests for assessment of sarcopenia are needed.

DOI: 10.1530/endoabs.65.P82

P83

Estimation of post-surgical hypoparathyroidism incidence following total thyroidectomy in University Hospitals Leicester NHS Trust

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Background
British Association of Thyroid and Endocrine Surgeons defines post-operative hypocalcaemia as adjusted calcium of < 2.0 mmol/l; 'late hypocalcaemia' as the ongoing requirement for calcium/Vitamin D supplements at 6 months; permanent post-surgical hypoparathyroidism (PSHP) at 12 months. The incidence rates of late hypocalcaemia are 6.5–12.1% and PSHP is 0.9%–4.5%.
Objective
To evaluate PSHP incidence rate in total thyroidectomy patients beyond 12 months post-operative period.
Methods
A list of consecutive total thyroidectomy cases was obtained from Histopathology department from 2010 to 2017 and retrospective evaluation of electronic records was undertaken. Adjusted calcium recorded at least 12-months post-operative period was considered.
Results
Over 8-year period, Out of 507, $n=201$ patients had total thyroidectomy; rest excluded due to lack of data or erroneous coding. $n=58$ post-operative hypocalcaemia (incidence 28.9%); $n=21$ (19F:2M)(incidence 10.4%) developed PSHP; mean follow-up 6.02 years. At diagnosis: Mean age 48-years; mean BMI 27.7 wt/ht^2; mean adjusted calcium 1.84 mmol/l (2.10–2.60); mean Parathormone 1.23 pmol/l (4–7); mean Vitamin-D 42 pmol/l (>50 is normal). 94%(19/21) treated with Vitamin D analogues (86% alfacalcidiol, 8% calcitriol) with or without calcium salts.
Discussion
Our retrospective analysis identified higher incidence rate of permanent PSHP (10.4%) similar to 2012 BAETS national audit (12.1%). Temporary hypocalcaemia incidence (28.9%) was similar to majority of studies (23–46%). Female sex, extended neck dissection, post-operative iodine ablation in thyroid cancer was identified as risk factors for PSHP. >60% had not had calcium level checked after 12 months and therefore unable to ascertain current calcium status.
Learning point
We feel that the incidence rates of permanent PSHP is higher than quoted in literature. Missed diagnosis can result in considerable morbidity and is potentially fatal. Close monitoring of calcium is recommended for a minimum period of 12 months to optimise detection and for timely management.

DOI: 10.1530/endoabs.65.P83

P84

A retrospective cohort study evaluating the relationship between the severity of vitamin D deficiency and the clinical and biochemical presentations of patients with primary hyperparathyroidism (PHPT)

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Background
Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder, with an estimated prevalence of 1 to 4 per 1000 in the general population. It is well established that vitamin D deficiency co-exists with PHPT. However, there are very few studies that looked at the relationship of the severity of vitamin D deficiency to the clinical and biochemical presentations of PHPT.
Aim
This study evaluated the prevalence of vitamin D deficiency and its relationship to the biochemical and clinical presentations of PHPT.
Methods
This observational cohort study employed a retrospective design where clinical records of 400 new patients referred to the metabolic bone clinics for investigation of hypercalcaemia, between 2010 and 2017, were reviewed. The study population was grouped as 'asymptomatic' or 'symptomatic' based on the absence or presence of at least one classical hypercalcaemia-related symptom. The relationship of the severity of vitamin D deficiency to the clinical and biochemical presentation of PHPT was evaluated.
Results
PHPT is more prevalent in women with female to male ratio of 4.4:1. Symptomatic patients were significantly younger compared to the asymptomatic group (60.97 year + 15.356 vs. 65.88 years + 13.924, $P=0.001$). There was a high prevalence of vitamin D deficiency (64.25%) with no difference between the symptomatic and asymptomatic groups. There was a significant inverse correlation between the level of vitamin D and PTH ($P=0.000$). There was a high prevalence of osteoporosis (53.35%) across of the entire study population with no between group differences.
Conclusion
Vitamin D deficiency is highly prevalent in patients with PHPT regardless of whether the patients were symptomatic or not. Symptomatic patients were younger compared with those without symptoms. The severity of vitamin D deficiency did not correlate to the severity of symptoms or prevalence of osteoporosis.

DOI: 10.1530/endoabs.65.P84

P85

The use of 2D-computed tomography scan as a first-line imaging modality in primary hyperparathyroidism

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Background
Minimally invasive parathyroidectomy relies on accurate localisation of the culprit gland. Combination of US plus Technetium 99m-sestamibi is considered the gold standard. CT parathyroid is thought to be a valuable tool in the pre-operative localisation.
Aim
To evaluate the diagnostic performance of 2D CT parathyroid in patients with primary hyperparathyroidism (PHP).
Methods
This was a single-institution prospective study of patients with PHP who underwent a combined imaging protocol of US and CT (US+CT) parathyroid from January 2017 to January 2019, with subsequent parathyroidectomy. Sestamibi was reserved for patients with diagnostic uncertainty. The reference standard for correct localisation was basis on intraoperative PTH, histology and biochemical confirmation on follow up (at least 6 months).
Results
Seventy-five patients were evaluated with combined US+CT. Total 54 (72.0%) had sestamibi of which 47 patients were referred with scan performed elsewhere. CT correctly identified a target in 63 (84%). In 17 patients CT was the only modality correctly localised parathyroid adenoma. The diagnostic accuracy of US+CT was superior to US and sestamibi (88% and 65% respectively; $P<0.001$). 21 patients (28%) had an ectopic adenoma, 9 (22%) had multi-glandular disease and 36 (48.0%) with parathyroid weighted <1.0 g. Within these subgroups, CT alone was superior to US+sestamibi for ectopic adenoma (82% and 57% respectively; $P=0.07$). The combination of US+CT increased accuracy to 86% $P=0.016$ for ectopic adenoma. CT showed higher sensitivity than US and sestamibi for smaller adenomas <1.0g (81% and 62% respectively, $P=0.04$). The correct pre-operative diagnosis of multi-glandular disease is most difficult, with similar accuracy for US+sestamibi and US+CT (40% and 50%, respectively, $P>0.99$).
Conclusion
The combination of US+CT provided a superior pre-operative localisation in 88% of patients, with relatively better diagnostic accuracy for smaller or ectopic adenomas and should be considered as a first-line imaging modality.

DOI: 10.1530/endoabs.65.P85

P86

Effect of vitamin D analogue therapy in a patient with autosomal dominant hypocalcaemia type 2 (ADH2) due to GNA11 p.Arg60Leu mutation

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Background
Autosomal dominant hypocalcaemia (ADH) is most commonly due to activating mutations in the Calcium Sensing Receptor (ADH Type 1), in which treatment with vitamin D analogues is frequently associated with hypercalciuria. More recently, activating mutations in the alpha-subunit of the G-protein α-11 (Gα11), encoded by *GNA11*, have been identified in a small number of ADH kindreds (ADH Type 2). The impact of vitamin D analogue treatment in ADH2 patients has not been evaluated.
Case Report
The proband, a 46-year-old female, was incidentally found to be hypocalcaemic. Clinical assessment revealed that she was experiencing intermittent paresthesia and cramping of the digits. Baseline biochemical testing confirmed a reduced serum corrected calcium (1.79 mmol/l; NR 2.1–2.55 mmol/l), raised serum phosphate (2.05; NR 0.8–1.5 mmol/l), low plasma PTH (1.0 pmol/l; NR 1.5–7.6 pmol/l), and low urine calcium:creatinine (U.Ca:Creat) ratio (0.2; NR 0.3–0.7). Her father had been on long-term calcium supplementation raising the possibility of a dominantly inherited hypocalcaemic disorder. Subsequent gene-panel testing revealed a pathogenic *GNA11* variant (c.179G>T; p.Arg60Leu) establishing the diagnosis of ADH2. The patient was treated with calcitriol (with $\geq$1000 mg dietary/oral calcium/day) to relieve hypocalcaemic symptoms and has been monitored for >21 months with serum and urine calcium measurements. The calcitriol dose was progressively increased from 250 ng daily to 1000 ng daily, which improved symptoms, and increased her serum calcium in a dose-dependent manner from 1.79 to 2.09 mmol/l. This was not associated with consistent alterations in serum phosphate or PTH. However, treatment with calcitriol 1000 ng daily increased her U.Ca:Creat ratio to 0.5 and was associated with hypercalciuria (24 hour urine calcium >0.1 mmol/kg per 24 h), despite failing to normalise serum calcium concentration.
Conclusions
Although vitamin D analogue therapy may alleviate symptoms and improve hypocalcaemia in patients with ADH2, caution is required as hypercalciuria may occur, even when serum calcium is below the reference range.

DOI: 10.1530/endoabs.65.P86

P87

Investigations in preparation for surgically managed primary hyperparathyroidism

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Background
Recent NICE guidelines[1] suggest imaging the parathyroid with ultrasound as first line prior to parathyroidectomy, MIBI as an alternative and surgical exploration if discordant. Investigation should also include a renal ultrasound and DEXA. This audit compares a single surgeon practice in one hospital to the guidelines.
Methods and Results
All patients with a parathyroidectomy performed by a single surgeon between July 2016 and July 2018 inclusive were eligible. Biochemistry and imaging was accessed from local hospital IT systems and compared to histology and post-op calcium as gold standard. 45 patients were eligible; 33 patients were included (exclusions: 10 tertiary hyperparathyroidism, 1 incomplete data, 1 repeat entry). 76% (n=25) had DEXA scans. 88% (n=29) had 24 h urinary calcium, (elevated in 52% (n=15)). 33% (n=11) of patients had a renal ultrasound (3 identifying renal calculi). All patients had parathyroid imaging: 36 MIBI +/− SPECT scans; 7 parathyroid ultrasounds performed by 4 sonographers. In patients with adenoma on final diagnosis (n=27), MIBI correctly identified adenoma in 28 cases 64% (n=18). 2/4 (50%) ultrasound identified a lesion. 18.5% (n=5) showed no concordance between investigations and operative findings. Full or partial concordance was achieved in 81.5% (n=22). Postoperatively, three patients remained hypercalcaemic despite parathyroid tissue removal (two diagnosed as sarcoidosis, despite elevated PTH; one under investigation) but surgery identified all other adenomas.
Conclusion
Renal US has traditionally only been used in those with high urinary calcium, due to low pick up rate of incidental renal stone disease. Surgery remains gold standard for identification of parathyroid lesions. MIBI detection rate was low which might reflect the mild disease considered for operation. Parathyroid US detection rate remains low (and infrequently used) contributed to by multiple operators. 4D-CT remains a useful addition when diagnostic doubt.
Reference
1. *Hyperparathyroidism (Primary): Diagnosis, Assessment and Initial Management*. London: NICE; 2019

DOI: 10.1530/endoabs.65.P87

P88

The prevalence of vitamin D deficiency in patients admitted with low trauma fractures – is pragmatic vitamin D supplementation appropriate?

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Aim
This study evaluated the prevalence of vitamin D deficiency in patients admitted with low trauma fracture (LTF). We also explored whether there was a rationale to offer appropriate and safe high dose vitamin D supplementation on admission for patients who are not already on vitamin D supplementation to avoid delay in commencing active bone protection treatment if required.
Patients and methods
Using the FLS database, 1460 patients over the age of 50 years seen and assessed during their in-patient admission between January 2015 and December 2017 were identified. Data on serum vitamin D level were collected and analysed.
Results
Of the 1460 inpatients seen by the FLS team, data on vitamin D results from 831 patients were included in the analysis. 629 patients were excluded as 331 did not have their vitamin D levels checked and 298 patients were already on vitamin D supplementation on admission. From the 831 patients, 68% (n=558) were female and 32% (n=273) were males. Using the National Osteoporosis Society classification, 19% of patients were vitamin D replete (serum vitamin D level of >50 nmol/l), 24% were vitamin D insufficient (serum vitamin D level of 31–50 nmol/l) and 57% were vitamin D deficient (serum vitamin D level of $<$ 30 nmol/l). Subgroup analysis showed that vitamin D deficiency is highly prevalent amongst patients of 60 years and over and those admitted with fractured neck of femur.
Conclusion
This study highlights the high prevalence of vitamin D deficiency in patients admitted with LTF. This finding raises the potential benefit of a pragmatic approach of offering this group of patients with reasonable and adequate loading dose of vitamin D without the need for testing. A follow up study to determine whether this regimen actually renders patients replete with vitamin D is now needed.

DOI: 10.1530/endoabs.65.P88

P89

Bone turnover marker response in patients on second line agents for osteoporosis – what is the significance of non-suppression?

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Background
Bone is constantly remodelling and an imbalance between bone resorption and formation can predispose to osteoporosis. Bone turnover markers (BMTs) are biochemical markers that reflect the dynamics of bone formation and resorption. Carboxy-terminal collagen crosslinks (CTx) is a bone resorption marker measured in serum which is used to monitor treatment response.

Aims
The aims of the study were to determine how CTx has been used to monitor patients following treatment with intravenous zoledronic acid and denosumab at Queen Elizabeth Hospital Birmingham and to assess the performance of bone turnover markers in clinical practice by assessing their use in monitoring treatment response.
Methods
Retrospective analysis of patient's records who completed a full course of zoledronic acid ($n=77$) or denosumab ($n=36$). Significant treatment response was defined as a reduction of the CTx concentration by more than 30% from baseline or post-treatment values in the lower half of the pre-menopausal range (<0.3 ng/ml) if no baseline measurements were present.
Results
For the zoledronic acid group, 60 patients (78%) had CTx measurements pre- and post-treatment or post-treatment only. Of these patients, 61% of patients showed a significant treatment response. Mean serum CTx pre-treatment was 0.34 ng/ml, falling to 0.21 ng/ml post-treatment ($P=0.05$). 30 patients (91%) in the denosumab groups had CTx measurements pre- and post-treatment or post-treatment only. 65% of these patients showed a significant treatment response. Mean serum CTx pre-treatment was 0.34 ng/ml, falling to 0.18 ng/ml post-treatment ($P=0.01$).
Conclusions
Following a full course of treatment serum CTx values decreased by 37% in the zoledronic acid group and 53% for the denosumab group. It remains to be seen whether those with significant reductions in CTx have lower fracture incidence. The study highlights that BMTs can be a useful measure of treatment response in clinical practice. Further follow up is required to assess impact on clinical outcomes.

DOI: 10.1530/endoabs.65.P89

P90

Rare case of pseudohypoparathyroidism Type 1b

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Pseudohypoparathyroidism (PHP) is highly heterogeneous rare disorder characterized by end organ resistance to PTH action with proven genetic component. PHP-Ib classically refers to a condition characterized by renal resistance to PTH in the absence of other endocrine or physical abnormalities and in the presence of a normal GNAS alfa activity and only few cases have been reported so far. We report a case of 43 year old gentleman was diagnosed to have seizures at the age of 13 and was commenced on anti-epileptic medication. During the work up for cataract at the age of 31, he was found to have low calcium. As his seizures were thought to be related to hypocalcaemia, his antiepileptic medications were stopped and he was commenced on alfacalcidol and calcium supplements. His older brother and nephews were also later found to have low calcium. His thyroid function and pituitary profile were within the normal range. He had elevated parathyroid hormone levels with normal 25 hydroxy vitamin D and normal adjusted calcium levels. On genetic testing, GNAS sequencing was normal but Methylation of GNAS showed complete loss of the maternal methylation pattern, confirming the diagnosis of pseudohypoparathyroidism type 1b, without the features of short stature, developmental delay and short metacarpals. PHP Ib is most often a sporadic disorder, but sex-linked autosomal dominant inheritance has been reported. In inherited cases, PTH resistance in PHP type 1B develops only after maternal transmission of the molecular defect, whereas paternal transmission of the defect is not associated with PTH resistance. This case emphasises the importance of appropriate referral and timely management as the diagnosis of such rare disorders is often delayed, leading to an initially inappropriate management.

DOI: 10.1530/endoabs.65.P90

P91

There is a need to improve care provision for primary hyperparathyroidism – results of a survey of *Parathyroid UK*

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Background
Anecdotal evidence suggests that access to surgical care for primary hyperparathyroidism (PHPT) varies significantly across the UK.
Method
A web-based survey was emailed to all members of *Parathyroid UK* patients' group.
Results
Replies were received from 119 patients (108F: 11M, median age 57) who have had a diagnosis of PHPT for a median for 5 years (3 months–10 years). Majority were diagnosed by their GP (63%) and 64% were initially offered no active treatment. 76% of respondents already had parathyroid surgery after a median of 2 years (range 6 months–over 5 years) after diagnosis. Vast majority (81%) described symptomatic improvement after parathyroidectomy but 32 patients reported unfavourable outcomes: failure to cure ($n=5$), anxiety/low mood ($n=3$), voice changes, hypocalcaemia, bone pain and muscle spasms, fatigue ($n=2$). Overall 84% of respondents would recommend surgery to another patient. 41 respondents didn't have parathyroid surgery either because they were still deciding ($n=9$), or as a result of advice form their own GP/Specialist ($n=15$) or their own decision ($n=4$) or because they were on a waiting list ($n=13$). The median *Pasieka's Parathyroid Symptom Score* did not differ between these subgroups. Responders made the following suggestions for improvements to current service provision: increasing the educational awareness for GPs and endocrine specialists on the diagnosis of PHPT, implementing a better communication system for patients to liaise with specialists regarding questions and worries they may have, increasing awareness of management of patients with normocalcaemic PHPT and increasing the availability of after-surgery care for patients.
Conclusion
Based on comments from a self-selected group of patients motivated to join a patients' support group, there is evidence that the current provision of care for PHPT needs to be improved. Recent NICE guidelines should facilitate this process but the responsibility has to be shared by all care providers.

DOI: 10.1530/endoabs.65.P91

P92

Hypercalcaemia management in in-patients in a district general hospital

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Background
Hypercalcaemia is a common finding in in-patients. Acute hypercalcaemia can be life-threatening; thus proper work-up is pivotal for correct assessment of underlying-cause and management. The European Hypercalcaemia Guidelines 2016 was used as reference.
Aim
Study was undertaken to assess appropriateness in work-up, diagnosis and management of patients with hypercalcaemia according to European Guidelines.
Methods
Patients diagnosed with hypercalcaemia between November 2017 and December 2018 admitted to a DGH across medical and surgical specialities were included in this retrospective study. Data was obtained from medical records for symptoms of hypercalcaemia and biochemical tests (including adjusted-serum-calcium; adj.S.Ca), and patients' detailed management plans.
Results
50 patients were included in the study, (17 males; mean age: 76.1 years. Hypercalcaemia was mild in majority of patients ($n=43$; 84%) (adj.S.Ca ≥ 2.67 <3.0 mmol/l); than moderate (adj.S.Ca ≥ 3 <3.5 mmol/l) ($n=5$;10%) and severe ($n=3$; 6%) (adj.S.Ca ≥ 3.5 mmol/l.) 31 patients (62%) demonstrated symptoms of hypercalcaemia. All patients had renal function tests assessed on admission, 98% had phosphate levels measured, but parathyroid hormone (PTH) measured in only in 19(38%) patients and Vitamin D in 32%. ECG was done in 24% and 1 patient had ECG changes. Of the patients who had PTH measured 52% had high PTH-levels, 31% had low, and 15% had normal PTH levels. Of those with high/normal PTH, 76% were referred to an Endocrinologist. 16% had known malignancy. 6% of patients with low PTH had malignancy. Management varied within the group: 14% received intravenous fluids, bisphosphonates 8%, Steroids 8%, Dialysis 2%. 74% had repeat adj.S.calcium after 24 h. No patient had 24 h urine-calcium. Management of hypercalcaemia was appropriate in 60% patients. Only 12% had follow-up with Endocrinology.
Conclusion
Guidelines are poorly followed in in-patients for assessment and management of hypercalcaemia. Training of health care professionals is crucial for delivery of best care to such patients.

DOI: 10.1530/endoabs.65.P92

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Lithium induced hypercalcaemia – local review of presentation, management and surgical outcomes

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Lithium induced hypercalcaemia can occur in 4.3–6.3% patients. Lithium interacts with CaSR in parathyroid gland and can 'unmask' parathyroid adenoma or cause parathyroid gland hyperplasia. It can cause tubular damage leading to tubular concentration defect or nephrogenic DI. Parathyroid hyperplasia in patients with LAH is much more prevalent than in PHPT.

Methods

The aim of this project was to review presentation and management in patients with diagnosis of 'Lithium induced hypercalcaemia' and 'Lithium associated hyperparathyroidism' presenting to secondary care during 2008–2018. Data was collected on cCa, PTH, presentation, presence of polyuria/DI, localisation investigations type of management lithium discontinuation/continuation and surgical outcomes.

Methods

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Results

30 patients were identified and divided into two groups. Group 1 (4/30)-those presenting with severe hypercalcaemia, but normal PTH. All presented acutely with severe AKI, lithium toxicity. Mean cCa – 3.01 mmol/l. All normalised with fluids, lithium omission, pamidronate. Group 2 (26/30) – those presenting with lithium associated hyperparathyroidism (LAH). 11/26 (42%) presented acutely, 9/26 (34%) had polyuria or confirmed DI. Mean cCa – 2.9 mmol/l, mean PTH-19 mU/l. 20/26 of patients with LAH were treated conservatively. 12/20 were able to discontinue lithium. cCa normalised in 7/12. 5/12 had ongoing hypercalcaemia. 2/5 started cinacalcet with cCa normalisation. 8 patients continued lithium and 3/6 fulfil criteria for cinacalcet. 4 out of 6 patients referred for surgery underwent surgery. 2/4 had explorative and 2/4 targeted parathyroidectomy. All had single adenoma.

Discussion

Lithium induced renal concentration defect and DI can contribute to significant hypercalcaemia during acute illness even in those without LAH. Lithium discontinuation resolved hypercalcaemia in 58% of conservatively managed patients with LAH. Cinacalcet seems to be an effective therapy in patients with LAH, but higher doses seem to be required. Contrary to literature, all patients who underwent surgery had single adenoma rather than hyperplasia.

DOI: 10.1530/endoabs.65.P93

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An audit on the surgical management of patients with asymptomatic primary hyperparathyroidism (PHPT) at University Hospital Birmingham

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Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder and contributes to excess morbidity and mortality in the populations affected. In developed healthcare systems PHPT is routinely diagnosed at the asymptomatic stage. Parathyroidectomy is the only curative treatment. The latest guidelines specific to the surgical management of patients with asymptomatic PHPT have been developed by the Fourth International Workshop. This audit aimed to establish how many of the new patient referrals with a clinical diagnosis of asymptomatic PHPT seen in the Metabolic Bone clinic at UHB tertiary care centre between 2015 and 2017 were referred for surgery in accordance with the Fourth International Workshop Guidelines. The clinical referral letters of all 216 patients with a confirmed diagnosis of PHPT were screened to find asymptomatic patients with sufficient data for analysis. 89 patients met this criteria. 21 patients with asymptomatic PHPT were referred for surgery. 76% were referred in accordance with the international guidelines. Of those patients not referred for surgery, 52.80% met at least one of the Fourth International Workshop criteria for surgery. In a significant minority of these cases,15%, the reason for non-referral to surgery was unclear. A proportion of patients in this category were aged <50 years and would be at highest risk of end organ damage resulting from hypercalcaemia. This audit demonstrates that adherence to international guidelines regarding the surgical management of patients with asymptomatic PHPT is suboptimal. It highlights the need for the implementation of comprehensive, standardised local protocols to improve this. Despite the subsequent publication of the May 2019 NICE guidelines on the diagnosis, management and initial assessment of patients with hyperparathyroidism, the requirements suggested in this audit specific to patients with asymptomatic PHPT require further consideration.

DOI: 10.1530/endoabs.65.P94

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A case of successful parathyroidectomy in the third trimester of pregnancy

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Primary Hyperparathyroidism (pHPT) affects approximately 1:2000 women under 40 years of age, so pHPT in pregnancy is uncommon. It is associated with significantly increased risks of morbidity for mother and foetus. Conventionally, surgery is recommended, ideally early in the second trimester. A 31-year-old woman attended the Accident and Emergency department at $26+4$ weeks of her third gestation, with severe loin pain and fever. She had a past medical history of pyelonephritis. Of note, her father had previously undergone parathyroidectomy for a parathyroid adenoma. On admission, the adjusted calcium level was found to be 2.94 mmol/l, phosphate level 0.35 mmol/l, PTH level 18.4 pmol/l, with hypercalciuria of 6.3 mmol/24hrs and evidence of acute kidney injury. A renal ultrasound scan revealed a left ureteric calculus measuring 1 cm, causing moderate left-sided hydronephrosis. A left nephrostomy stent was inserted relieving the obstruction. Serum calcitonin and fasting gut hormone levels were normal. Genetic testing for Multiple Endocrine Neoplasia is underway. With aggressive intravenous rehydration, the adjusted calcium level normalised to 2.49 mmol/l, but rose again to 2.76 mmol/l. In the context of the evidenced end-organ damage due to hypercalcaemia, a decision was made to perform parathyroidectomy at $30+3$ weeks of gestation. Pre-operative intravenous steroids were administered, to minimise foetal risk. Ultrasound scan of the neck revealed two suspected parathyroid adenomas. At surgery, 3 parathyroid glands were removed and the intraoperative PTH level decreased from 70 to 7 pmol/l. Post-operatively, the adjusted calcium level was 2.17 mmol/l initially and 2.29 mmol/l subsequently. The procedure was uneventful. Parathyroidectomy in pregnancy needs to be carefully planned and discussed with an expert multidisciplinary team, particularly with regards to optimal perioperative care and timing, in order to minimise risk to mother and foetus, including miscarriages, pre-eclampsia and neonatal tetany.

DOI: 10.1530/endoabs.65.P95

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Primary hyperparathyroidism in pregnancy – successful pregnancy outcomes in a series of five cases

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Primary hyperparathyroidism is rarely diagnosed in pregnancy; not only because it is uncommon in that age group but also because many of the symptoms overlap with non-specific pregnancy symptoms (nausea, vomiting, fatigue, constipation). Primary hyperparathyroidism with significant hypercalcaemia can potentially cause serious maternal (preeclampsia, nephrolithiasis, pancreatitis and hypercalcaemic crisis) and foetal (miscarriage, stillbirth, neonatal hypocalcaemia leading

to tetany and rarely long term hypoparathyroidism) complications. We present a series of five primary hyperparathyroidism cases; all of whom had successful pregnancy outcome. Only one case was diagnosed before conception. This was managed conservatively during pregnancy as corrected calcium was 2.71 mmol/l at diagnosis and remained in the same range throughout the pregnancy. PTH was (6.1 pmol/l, reference range 1.6–7.2) and familial hypocalciuric hypercalcemia (FHH) was excluded. Her hypertension has persisted post-pregnancy and she is awaiting parathyroidectomy. Of the other four cases, all were diagnosed during pregnancy and all had corrected calcium levels at diagnosis greater than 3.0 mmol/l. Two cases were diagnosed during the second trimester (at 18 and 24 weeks) and had parathyroidectomy respectively during week 24 and 28 of gestation. The other two cases were diagnosed during the third trimester (at weeks 30 and 32) and were closely monitored throughout the remainder of the pregnancy. Both underwent parathyroidectomy post-partum. Four of five women were South Asian, four of five were in their mid to late thirties and four of five were deficient in vitamin D at diagnosis. None of the neonates had hypocalcaemia.

DOI: 10.1530/endoabs.65.P96

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Prevalence of PPI usage amongst patients with severe hypomagnesaemia in a London hospital

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The association between hypomagnesaemia and proton pump inhibitors (PPIs) has been well-established in recent years, with a median onset of electrolyte disturbance around 5.5 years after PPI initiation. The mechanisms and aetiology of this potentially life-threatening side-effect remain unclear. We assessed the prevalence of PPI usage in all cases of severe hypomagnesaemia (defined for the purposes of the study as a magnesium level <0.4 mmol/l) in our hospital over the course of 12 months between April 2017 and April 2018. In total, there were 160 cases, excluding children aged 16 or under. None of the patients had Gitelman's syndrome. All but six patients were admitted at the time of the measurements. Twenty-one patients (13.1%) died during their admission; 6 patients had no discharge letter written and hence no accurate medication history was obtainable. Of the remaining 127 patients, 95 (74.8%) were on a PPI at the time of admission. The PPI was stopped in only 20 (15.7%) of these patients. Severe hypomagnesaemia and need for intravenous correction was only mentioned on the discharge letters of 48 patients who survived to discharge (38.8%). Only fifteen of the patients were admitted under the endocrine team and all of those had their PPI stopped; thirteen patients were admitted under local surgical teams, with the remainder under a variety of other medical teams. The data highlights the need for greater awareness of this effect of PPIs in our hospital, especially among non-endocrine specialty teams.

DOI: 10.1530/endoabs.65.P97

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Audit into appropriate diagnostic investigation and MDT discussion prior to parathyroidectomy for primary hyperparathyroidism

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An audit of parathyroidectomies carried out at the East and North Herts Trust between 2010 and 2014 revealed a 25% failure rate following surgery. The audit revealed inappropriate pre-operative workup with regards to biochemistry and/or imaging in 40% of cases. In 2015, a parathyroid MDT was established. The aim of this was to ensure patients had appropriate investigation prior to referral for surgery. A Trust hyperparathyroidism pathway was written based on best practice and available evidence. The guideline advocated full initial biochemical workup and exclusion of alternate diagnoses. Imaging (USS and standard Sestamibi) was to be carried out if the biochemistry was in keeping with primary hyperparathyroidism and if the patient was a candidate for surgery. If there was discordance in imaging, a SPECT CT was performed. All patients were discussed at the MDT. An audit of the first three years revealed a significant improvement in outcome (0.05–0.15% failure rate following surgery). The audit also demonstrated a benefit of third line imaging, in particular, SPECT CT. In cases where there was discordance between USS and Sestamibi (33% of cases), where a SPECT CT was carried out, this led to gland localisation in the majority of cases and this in turn led to localized surgery and a successful outcome. Of interest, despite the reported rarity of familial hypocalciuric hypercalcaemia (FHH), a significant prevalence of this disorder was recognised with 5 new cases of FHH1 and the rarer FHH3 diagnosed. New NICE guidelines for hyperparathyroidism assessment and management suggest MDT discussion only if patients have unsuccessful surgery. However, this audit demonstrates the benefits of pre-surgery MDT and the significant improvement in outcome.

DOI: 10.1530/endoabs.65.P98

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Normocalcaemic primary hyperparathyroidism: a diagnostic dilemma

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Due to availability of easy routine blood testing, normocalcaemic primary hyperparathyroidism is increasingly seen. However, due to its mild nature, it often poses diagnostic difficulties. We present a case of 65 year old gentleman who was diagnosed with osteoporosis in 2015. He had a history of traumatic fractures of tibia, fibula and calcaneum in 2013. He was later diagnosed with unexplained osteoporosis in 2015 (T-score of hip -2.5 and T-score of spine -1.2) and was treated with alendronate, which was stopped two years later. He was subsequently found to have elevated PTH with normal calcium and phosphate levels (calcium 2.48 mmol/l, PTH 15 pmol/l, vitamin D 121 nmol/l and phosphate of 1.0 mmol/l). His calcium creatinine ratios were 0.0133 and 0.0144. These results were likely to be complicated by previous bisphosphonate therapy. Genetic testing for familial hyperparathyroidism and multiple endocrine neoplasia was negative. His localization studies were negative. Therefore, in order to support the diagnosis of primary hyperparathyroidism, it was decided to proceed with calcium loading test during which he was given one gram of elemental calcium and his PTH, plasma and urinary calcium were measured every hour. His calcium increased from the baseline of 2.45 mmol/l to 2.61 mmol/l which supported the autonomous production of PTH secretion. In view of osteoporosis, he underwent bilateral neck exploration resulting in parathyroidectomy. The histology revealed the parathyroid adenoma and his PTH normalized after surgery. Calcium loading test has been described in the literature for diagnosing normocalcaemic and borderline cases of primary hyperparathyroidism. Although, it is not routinely performed, it can be useful in the diagnosis in such clinical settings.

DOI: 10.1530/endoabs.65.P99

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Management of Familial Hypophosphatemia in Pregnancy

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Familial Hypophosphatemia is an inherited disorder of bone metabolism that affects 1 in 20 000 new-borns. The X-linked dominant form of the disease results from a genetic mutation of the PHEX gene. This leads to disordered regulation of fibroblast growth factor 23 resulting in reduced phosphate renal reabsorption and vitamin 1α Hydroxylation. Clinical features include short stature, rickets, craniosynostosis and dental abnormalities.

Case

A 29 year old woman was referred to the joint Antenatal endocrine clinic at 28 weeks gestation. She was diagnosed with familial Hypophosphatemic rickets in childhood of which a mutation in the PHEX(Phosphate regulating gene with homology to endopeptide on X chromosome) gene was identified . This was an x-linked dominant pattern of inheritance. Her mother was also diagnosed with the

condition however her brothers were not affected. At 20 weeks gestation, the growth scan showed no significant abnormalities apart from the foetus measuring slightly small for dates. Progressive growth of femur length and head circumference were subsequently noted on serial growth scans. She was managed with Phosphate Sandoz and alfacalcidol 50 mcg daily. Her average calcium was 2.39 mmol/l (2.20–2.60 mmol/l), Phosphate 0.81 mmol/l (0.80–1.50 mmol/l). Vitamin D was normal at 66 nmol/l. She delivered at a healthy female infant at 39 weeks gestation.

Discussion

Familial X-linked dominant hypophosphatemic rickets confers a 50% chance of transmission to offspring. The implication of this means that if the gene defect is inherited, potential disorders in bone growth and development could occur. Genetic counselling was sought prior to conception. However following delivery, genetic testing of the infant might be required especially if there are physical manifestations of the disease. The aim of treatment in pregnancy is to ensure adequate phosphate and vitamin D levels to facilitate normal growth and development of foetal bones by treatment with oral phosphate supplements and calcitriol.

DOI: 10.1530/endoabs.65.P100

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Four cases of familial hypocalciuric hypercalcaemia presenting with severe hypercalcaemia

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Familial hypocalciuric hypercalcaemia (FHH) usually manifests with mild asymptomatic hypercalcaemia. Presentations with severe hypercalcaemia are uncommon and may be mistakenly assumed to be primary hyperparathyroidism (PHPT) unless detailed testing is undertaken on all cases of hypercalcaemia. We present 4 cases of FHH presenting with severe hypercalcalcaemia, corrected serum calcium (coCalcium) > 3 mmol/l. Three cases were initially admitted to hospital as medical emergencies. 2 cases were initially misdiagnosed as primary hyperparathyroidism and underwent 3.5 gland parathyroidectomy.

Case 1

40 year old lady, initial coCalcium 3.5. Diagnosed as PHPT. Underwent 3.5 gland parathyroidectomy. Subsequent persistent hypercalcaemia around 3. Histology of all surgical specimens was parathyroid hyperplasia, no adenoma. Further investigations suggested FHH. Genetic testing confirmed homozygous FHH1: calcium sensing gene mutation. Normal kidney function, normal bone density scan and renal ultrasound.

Case 2

50 year old man, initial CoCalcium around 3.5. Diagnosed as PHPT. Underwent 3.5 gland parathyroidectomy. Subsequent persistent hypercalcaemia around 2.75. Histology of all surgical specimens was parathyroid hyperplasia, no adenoma. Further investigations suggested FHH. Genetic testing: heterozygous FHH1: calcium sensing gene mutation. Normal kidney function, normal bone density scan and renal ultrasound.

Cases 3 and 4

63 year old man and his 37 year old son. Both presented with initial CoCalcium 3.1–3.2. Investigations showed low urine calcium excretion in father but not son. Genetic testing showed FHH3 due to adaptor protein 2 sigma subunit (AP2S) mutations in both.

Conclusion

Severe hypercalcaemia should not be assumed to be due to PHPT. All cases should have detailed investigation including calculation of the calcium to creatinine clearance ratio on a 24 h urine collection. If there is any diagnostic uncertainty then available first degree relatives should be screened for hypercalcaemia and molecular genetic testing performed. Homozygous FHH may present in adult life. FHH3 more frequently causes severe hypercalcaemia.

DOI: 10.1530/endoabs.65.P101

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Parathyroidectomy outcomes for primary hyperparathyroidism over a 2 year period at East Sussex Hospitals Trust

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Introduction

An audit of outcomes and indications for parathyroidectomy was conducted from April 2016 to April 2018 for all patients had primary hyperparathyroidism at East Sussex Hospitals Trust.

Methods

Clinical notes, pathology results and radiology results were accessed to compile the dataset. Indications for surgery were based on the National Institute of Health criteria for parathyroidectomy in hyperparathyroidism from 2013.

Results

62 patients were included in this audit (76% female). Most patients were aged 50–79 (79%) but the range was from 19 to 84. The most common presentation was as an incidental finding (44%) followed by bone pain (16%) and lethargy 13%). The average corrected calcium at presentation was 2.83 (range 2.58–3.30) with an average duration of hypercalcaemia of 35 months (range 4–100). 58 patients (94%) had urinary calcium measured and 29% fractional excretion of calcium. 61 patients (98%) had at least one NIH criteria for parathyroidectomy. Imaging showed that the US was positive in 56 (90%) patients, MIBI/SPECT 60 (97%) patients with localisation in 58 (94%) patients. There was a 92% correlation between imaging and surgical localisation. 59 (95%) patients had minimally invasive surgery and all were followed up by the surgeon and endocrinology. 53 patients had resolution of hypercalcaemia with surgery. 7 patients had second surgery with calcium normalisation and 2 were on the waiting list for redo surgery. 1 (1.6%) patient had malignancy while 61 (98.6%) had an adenoma. 1 patient suffered with vocal cord palsy that resolved within 2 months.

Conclusion

Since the last audit radiographic and surgical concordance has increased with the use of SPECT/MIBI from 92% to 94%. Surgical success increased from 93% to 97%.

DOI: 10.1530/endoabs.65.P102

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A case of severe hypercalcemia detected in early pregnancy

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Primary hyperparathyroidism (PHPT) is a common endocrine condition. Outside of syndromic presentations, it is relatively rare in young people and during pregnancy. The diagnosis in pregnancy poses a unique challenge and is often missed as the symptoms of hypercalcemia mimic those in pregnancy. We present a case of a 20-year old woman who was found to have severe hypercalcemia after she had persistent vomiting in early pregnancy. Biochemistry showed adjusted calcium of 5.34 mmol/l (2.2–2.6 mmol/l), parathyroid hormone of 103.9 pmol/l (1.6–6.9 pmol/l) and normal Vitamin D. Further investigations revealed hypercalciuria, impaired renal function and extensive renal medullary calcification. There was no family history of hypercalcaemia and no clinical or biochemical evidence of multiple endocrine neoplasia. She was fluid resuscitated aggressively. She decided to undergo medical termination of this unplanned unwanted pregnancy at seven weeks gestation and was subsequently commenced on cinacalcet. Despite this, hypercalcaemia remained refractory. Neck ultrasound and SESTA-MIBI failed to localize a parathyroid lesion. Subsequent 4D CT and C-11 methionine PET revealed a large mediastinal mass. She had parathyroidectomy at a thoracic surgery centre and histology revealed parathyroid adenoma embedded within thymic tissue. Calcium and parathyroid hormone normalized after surgery. This case highlights the challenges in diagnosis, investigation and management of hypercalcemia due to PHPT during pregnancy. The diagnosis is often delayed and needs a high index of suspicion. In our case, detailed probing revealed an 18-month history of generalized weakness, polyuria, nocturia, vomiting, and memory impairment. Localization of abnormal parathyroid gland/s is difficult in pregnancy as ultrasound is the only safe imaging technique and, when used alone, has low sensitivity. Most calcium-lowering drugs are contraindicated, with rehydration being the mainstay of treatment. If parathyroidectomy is indicated, it is best performed in the second trimester when organogenesis is complete and the risk of preterm delivery relatively low.

DOI: 10.1530/endoabs.65.P103

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Vitamin D Questionnaire Validation and exploration of association with serum 25-hydroxyvitamin D in a UK adult population: a cross-sectional study and pilot study

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Aims
To validate the questionnaire designed by O'Connor *et al*. (2018) and investigate the association between vitamin D knowledge and serum 25-OH-D.
Methods
Face and content validity were assessed by a panel of experts and public ($n=8$). The final questionnaire comprised of four sections; demographics (12 questions), knowledge (13 questions), attitudes toward sun exposure and vitamin D (11 questions) and perceptions of supplementation and fortification (four questions). Construct validity was assessed by employing 'known-groups' approach. Internal consistency was examined via Cronbach alpha ($\alpha \geq 0.70$) and factor analysis. Approximately two-weeks after the first questionnaire administration, the questionnaire was re-distributed for test–retest reliability. A sub-population was recruited and serum 25(OH)D was measured via blood-spot and LCMS analysis. Further descriptive statistic, *t*-test analysis, Chi-square and Kendall's tau-b correlation were performed (significance taken at $P<0.05$).
Results
190 individuals completed the first-round questionnaire, and $n=62$ completed the second-round online (Online Surveys). Content and face validity resulted in nine items reformulation. Factor analysis revealed the knowledge construct contained three components that had eigenvalues values >1, explaining 29.1%, 34%, 37.5%, of the total variance. Internal consistency was adequate (Cronbach $\alpha=0.786$). Construct validity was adequate (68.32% ($\pm$15.24) vs. 38.06% knowledge score ($\pm$14.19), $P<0.001$). Test–retest identified one knowledge question answer (($\chi^2(1)=1.032$, $P=0.040$) and two answer options ($\chi^2(1)=8.267$, $P=0.040$ and $\chi^2(1)=5.905$ $P=0.015$)) to have statistical significant answer distributions. A non-significant, moderate, positive association between knowledge score and serum 25-OH-D was identified ($n=10$, $\tau b=.333$, $P=.180$).
Conclusion
The questionnaire can be used as a validated instrument to assess vitamin D knowledge, attitudes and perceptions within research. Moreover, the pilot study demonstrates vitamin D knowledge is associated with vitamin D status, however, requires further research to verify this relationship.

DOI: 10.1530/endoabs.65.P104

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Complications at diagnosis in primary hyperparathyroidism

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Introduction
Primary hyperparathyroidism (PHPT) is associated with adverse effects especially on the bones and kidney. While nowadays it is mostly diagnosed at an asymptomatic stage, patients with overt involvement of the target organs at the time of diagnosis are still encountered.
Aim
To explore the frequency of disease complications already present at the time of diagnosis in a cohort of patients with sporadic PHPT who meet the current surgical guidelines criteria.
Material and methods
We retrospectively selected a cohort of patients consecutively diagnosed with PHPT in whom surgical intervention was recommended. We collected from patients' files biochemical and medical history data.
Results
54 patients (50 women-92.6%, 4 men) with a median age of 64 years (28–75) with sporadic PHPT were included. The serum calcium level ranged between 9.7–19.2 mg/dl (median 11.5) with a corresponding PTH level between 72.4–10 370 pg/ml (median 185.3). Serum 25OHD level was 4–26 ng/ml (median 14 ng/ml). The most frequent complications at diagnosis were osteoporosis, kidney stones, decreased estimated glomerular filtration rate (eGFR). 48.38% of cases had a lumbar-spine T-score <-2.5 S.D. ([−4.2;0.2], median −2.5) and the percentage was 52.35 for distal third radius ([−5.1;0.47], median −2.6). 5.6 % of patients had prevalent fragility fractures. eGFR was also affected in many cases: only 25% of patients had a GFR>90 ml/min and 41.67% between 60 and 90 ml/min; 57.4% had kidney stones.
Conclusions
Despite the increased use of screening methods aimed to diagnose early-stage PHPT, the rate of complications at the time of diagnosis in patients with surgical indications is still elevated.

DOI: 10.1530/endoabs.65.P105

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Are you kidney-ing me? An evaluation of methods to estimate renal function in the Mineral metabolism clinic

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Background
Directly measuring kidney function is time-consuming, expensive and impractical. Thus different formulas have been developed for estimating the glomerular filtration rate (eGFR) which provides a surrogate marker of clearance. The MDRD equation is commonly used to provide eGFR to clinicians. However, most product information suggests prescribing based on the estimated creatinine clearance (eCrCL) based on the Cockcroft–Gault (CG) formula. different equations utilise different factors in their equations, and thus have different accuracy in different patients groups. It the cohort of patients seen in the Mineral metabolism clinic, patients with increasing age and a lower weight tend to be common, compared to the average age of patients on which these equations were based. We thus set out to see how our prescribing would be influenced by different methods to estimate kidney function.
Methods
This study built on a previous pilot analysis. 100 patients given Zolendronic acid over 5 years in the mineral metabolism clinic were retrospectively selected and various parameters assessed. The eGFR was calculated using the MDRD equation and CKD EPI, and an eCrCl was calculated using the CG formula – with or without modification for BMI (when available).
Results
7 patients were found to have a eCrCl below the acceptable level for Zolendronic acid using the generic CG formula, and 9 using a Corrected eCrCl taking into account BMI. Some patients showed a temporary elevation of creatinine, but this normalised over time. In general the MDRD and CKD-EPI gave a higher eGFR, especially in older and lower BMI patients, compared to the CG formula.
Recommendations
Age and weight of individuals,as well as the strengths and limitations of different formulas, should be considered when prescribing medications in the mineral metabolism clinic. This may decrease the risk of nephrotoxicity and other side effects.

DOI: 10.1530/endoabs.65.P106

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Not all cases of hypercalcemia with calcium above 3.0 mmol/l and raised parathyroid hormone levels are due to primary hyperparathyroidism

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Parathyroid hormone-dependent hypercalcaemia is one of the commonest conditions seen in endocrinology clinics. Primary hyperparathyroidism (PHPT) is the usual cause although some cases are due to other conditions including familial hypocalciuric hypercalcaemia (FHH). Making the distinction between PHPT and FHH is important in order to avoid unnecessary parathyroid surgery. Urinary calcium quantification is an integral part of diagnostic investigations. We present the case of a 28 year lady who was suspected to have delayed growth as early as nine months of age. She was found to have significant hypercalcaemia (more than 3.0 mmol/l), hypophosphataemia and hyperparathyroidism but, apart from bothersome constipation, remained largely asymptomatic in childhood. She had no obvious family history of hypercalcemia. Further investigations showed normal vitamin D and urinary calcium with no evidence of renal calcification on imaging. Genetic testing for FHH revealed no mutation in CaSR gene. Further testing revealed a heterogeneous mutation of R15L in AP2S1 gene, confirming a

diagnosis of FHH type 3. At 24 years of age, a DEXA revealed osteopenia. She is currently under close endocrine surveillance with regular clinical assessments, biochemical monitoring for hypercalcaemia and hypercalciuria, renal imaging for nephrocalcinosis/nephrolithiasis and monitoring of bone mineral density. FHH is an autosomal dominant condition. Genetic defects in FHH result in reduced calcium sensing by parathyroid receptors with compensatory hypercalcemia and inappropriately low to normal urinary calcium. Patients are usually asymptomatic and require no active treatment. Mutation of the AP2S1 gene is a recognised cause of FHH type 3 and patients may have significant hypercalcaemia with non-suppressed parathyroid hormone. Cinacalcet has been successfully used in some FHH type 3 patients with symptomatic hypercalcaemia but there is no evidence that it has long term beneficial effects on bones or kidneys.

DOI: 10.1530/endoabs.65.P107

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An elusive cause of severe, recurrent hypercalcaemia

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Introduction
Primary skeletal muscle lymphomas are extremely rare, accounting for less than 1% of extra-nodal lymphomas.[1] Hypercalcaemia is a common reason for admission to hospital. There are four main mechanisms by which neoplasms can cause hypercalcaemia; secretion of parathyroid hormone-related peptide, osteolytic metastases, (rarely) ectopic PTH secretion, and expression of 1 alpha hydroxylase, causing excess activated vitamin D and gastrointestinal absorption of calcium.[2] We present a case of primary skeletal muscle lymphoma initially presenting with hypercalcaemia of unclear aetiology.
Case
A 78 year old female with a background of hypertension and CKD4 presented to acute medicine at the Queen Elizabeth University Hospital in an acute confusional state and was found to have a severe hypercalcaemia with an adjusted calcium of 3.90 mmol/l (ref. range 2.10–2.60). Serum PTH was within the reference range. CT of chest, abdomen and pelvis showed no evidence of malignancy. An isotope bone scan was unremarkable. This was treated with intravenous fluid hydration, furosemide and bisphosphanate with restoration of normocalcaemia and she was discharged with outpatient follow-up. Between outpatient visits she developed further episodes of significant hypercalcaemia (>3.0 mmol/l) which were responsive to high-dose steroids. Parathyroid subtraction scan did not demonstrate a parathyroid adenoma. 25-OH Vitamin D (the standard assay in our hospital) was normal. 1,25 OH Vitamin D was grossly elevated at 257 pmol/l. FDG PET-CT demonstrated a highly avid mass involving the left thigh and knee. Biopsy of the lesion confirmed primary B cell lymphoma of skeletal muscle.

DOI: 10.1530/endoabs.65.P108

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Severe acute 'non-malignant' hypercalcaemia

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A 56 year old man was admitted to hospital with a two day history of nausea and vomiting. Admission calcium was 4.1 mmol/l with a PTH of 146.5 pmol/l and creatinine of 227 umol/l. Primary hyperparathyroidism was diagnosed 4 months earlier with a calcium of 3.22 mmol/l and PTH of 24.4 pmol/l. He had prior outpatient treatment with intravenous disodium pamidronate and cinacalcet. He was waiting SPECT CT due to indeterminant imaging. Past history included right tonsillar carcinoma in 2004 treated with surgery including right neck dissection, chemotherapy and radiotherapy. Initial treatment was intravenous normal saline 0.9% 166 ml/h and plan for disodium pamidronate if eGFR >30. Within 24 h, calcium rose to 4.35 mmol/l and creatinine was 320 umol/l. Fluids were increased to 250 ml/h. Ultrasound of renal tract was unremarkable and urine output good. Pharmacy consulted the Renal Drug Handbook and noted that the same dose of disodium pamidronate could be given as in normal renal function if GFR was above 10 ml/min. Calculated creatinine clearance was 22 ml/min and patient was prescribed 90 mg in 500 ml normal saline 0.9% over 5 h. After discussion with endocrine surgeons, transfer was arranged for urgent SPECT CT and parathyroidectomy. SPECT CT revealed a 3.2 cm left sided parathyroid adenoma. Four days post pamidronate, calcium was 2.82 mmol/l and creatinine 248 umol/l. Surgery was performed the following day. Histology was consistent with parathyroid adenoma. Post operatively, there was a rapid improvement in renal function, almost normalising by 3 weeks. He remains normocalcaemic with GFR 81 more than 12 months later. This case highlights the need for intensive medical and surgical treatment in severe hypercalcaemia due to parathyroid disease, and also the use of the renal drug handbook.

DOI: 10.1530/endoabs.65.P109

P110

Hyperparathyroidism in pregnancy: a case series

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Introduction
Hyperparathyroidism in pregnancy is rare and is associated with significant maternal and fetal morbidity and mortality. Recognition can be challenging due to the inability to differentiate hypercalcaemia symptoms from those of pregnancy, studies suggest that up to 80% of cases may be undiagnosed. We report three cases of hyperparathyroidism in pregnancy at Royal Derby Hospital, investigations (Table 1) and management in these patients are reviewed.

Table 1

Investigation at presentation	Case 1	Case 2	Case 3
Corrected Calcium (mmol/l)	2.98	2.74	3.10
Parathyroid Hormone (ng/l)	32	52	54
Vitamin D (nmol/l)	54	71	30
PTH-Related Peptide (pmol/l)	1.4	–	5.0
Calcium Excretion Index (<15 suggests FHH)	46	24	90

Case 1
29 year old, 36 weeks pregnant (36/40) referred to endocrine clinic with incidental hypercalcaemia; diagnosed as hyperparathyroidism with low vitamin D. Vitamin D was replaced and calcium levels controlled with fluids. Post pregnancy, ultrasound neck revealed evidence of likely right inferior parathyroid adenoma and neck exploration surgery was scheduled.
Case 2
27 year old, 10/40 diagnosed with hypercalcaemia secondary to hyperparathyroidism. This was regularly monitored throughout pregnancy, controlled with oral fluid intake and calcium did not exceed 2.86 mmol/l. A left inferior parathyroid adenoma was excised *post-partum*, histology revealed this to be benign and calcium levels normalised post operatively.
Case 3
20 year old, incidental finding of hypercalcaemia at 24/40. Ultrasound neck revealed no evidence of parathyroid adenoma. Emergency caesarean section was required at 32/40 due to persistent hypercalcaemia (3.27 mmol/l) despite treatment with Cinnacalcet and Calcitonin.
Conclusion
Hyperparathyroidism during pregnancy is associated with suppression of neonatal parathyroid hormone and therefore risks severe neonatal hypocalcaemia, with a reported 30% mortality rate. It is therefore imperative to efficiently investigate and optimise management of hyperparathyroidism during pregnancy as in the cases described in order to minimise maternal and fetal complications.

DOI: 10.1530/endoabs.65.P110

P111

Hypophosphatasia in an infant: a differential diagnosis that should not be overlooked

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Introduction
Hypophosphatasia is a very rare inherited condition due to *ALPL* variants and is associated with a variable presentation.
Case description
The index case initially presented at 7 months with bulging anterior fontanelle, failure to thrive and mild developmental delay. She was born at 34 weeks gestation and had amniotic bands causing digital anomalies. She was sitting at 8 months, crawling by 15 months and a hearing test was normal. An MRI head following her initial presentation revealed craniosynostosis and further investigations confirmed intracranial hypertension (ICH), which led to posterior cranial vault distraction at 10 months. Despite this, repeated intracranial pressure monitoring demonstrated persistence of ICH. Of note, preoperative respiratory testing was normal. At 13 months, she had premature loss of 2 deciduous teeth with intact roots and her mother, who is a dental healthcare worker, raised concerns about a bone disorder. Osteopenia and metaphyseal flaring were evident on a left foot and chest X-ray at 4 months and 17 months respectively. At first presentation to the endocrine service at 16 months, her parents also reported possible arm and wrist pain. Other features on examination included a pectus carinatum, prominent eyes, square face and mild rhizomelia. She was also noted to have a persistent pupillary membrane and distended optic nerve sheaths. A micronutrient screen and metabolic and urinary bone screen, including vitamin D and PTH, were normal. However, she had persistently low ALP levels in the range of 29–67 U/l (>100). PLP was markedly raised at 1168 nmol/l (20–140), PLP/PA ratio was 22.9 and pyridoxic acid result was 51 nmol/l (9–60), confirming the diagnosis of hypophosphatasia. Genetic testing of 9 craniosynostosis variants was negative and *ALPL* analysis results are awaited.
Discussion
This case highlights the difficulties in diagnosing infantile hypophosphatasia and the need for maintaining a high index of suspicion and low threshold for detailed investigations.

DOI: 10.1530/endoabs.65.P111

P112

Recurrence of hypercalcaemia more than ten years following parathyroidectomy, was it an unfortunate coincidence or should we routinely follow up high risk patients for a longer period following parathyroidectomy

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Context
Parathyroid carcinoma is a very rare malignancy. It arises as a separate structure rather than from a pre-existing parathyroid adenoma. It may be difficult to differentiate it from parathyroid adenoma based on histology. When evaluating primary hyperparathyroidism clinical correlation should be taken into account. Clinical features of parathyroid carcinoma may include male gender, palpable neck nodule and higher parathyroid hormone and serum calcium levels associated with symptoms of hypercalcaemia.
Case description
A 67-year-old gentleman was diagnosed with primary hyperparathyroidism in 2007. He had raised adjusted calcium and PTH on routine blood test. An ultrasound of the neck did not identify any parathyroid adenoma but a SESTAMIBI scan raised the possibility of one. He had neck exploration surgery with left superior parathyroidectomy in January 2008. Following surgery his adjusted calcium and PTH were back to normal levels. Tissue histology revealed features of parathyroid adenoma with no malignancy. He was discharged from clinic follow-up but his GP was advised to check his serum calcium annually. He re-presented in March 2018 with raised adjusted calcium and PTH. Ultrasound revealed an enlarged parathyroid gland in the lower pole of the left thyroid lobe which was confirmed on SESTAMIBI scan. He went on to have a left inferior parathyroidectomy in August 2018 without resolution of hypercalcaemia. Postoperative histopathology has confirmed parathyroid carcinoma. He then had further surgical interventions including excision of parathyroid glands on both sides of the neck, left thyroid lobectomy and level VI clearance but with persistent hypercalcaemia. He has now been referred for adjuvant radiotherapy.
Conclusion
Histopathology examination may fail to confirm parathyroid malignancy following parathyroidectomy. The presence of some clinical features as mentioned above should raise the alarm bell and warrant regular and longer calcium monitoring post operatively even if the postoperative histopathology examination revealed no evidence of parathyroid carcinoma.

DOI: 10.1530/endoabs.65.P112

P113

Sarcoidosis imitating metastatic colon carcinoma

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We believe this is the first case report of anunusual presentation of hypercalcemia due to sarcoidosis mimicking metastatic colon carcinoma. A 68 year old lady with a background history of pancolectomy and neoadjuvant chemotherapy for Duke C1 rectal carcinoma under surveillance, ulcerative colitis, type 2 diabetes mellitus presented to the clinic with hypercalcemia with low parathyroid hormone (PTH) and symptoms of tiredness. Her blood test showed Adj Ca of 2.8 mmol/l, PTH < 2.5 pmol/l, Vitamin D 18 mol/l, ALP 177 U/l. She was commenced on 800 IU of vitamin D, ordered for bone scan, 24 h urine calcium excretion ratio, myeloma screen. Her surveillance CT scan couple of months earlier was reported stable features. She had an acute medical admission with unsteadiness of gait, tiredness and nausea. The adjusted calcium level was reported as 3.6 mmol/l with suppressed PTH. She was resuscitated with intravenous fluids and bisphosphate infusion. A CT scan of abdomen, chest and pelvis was organised that showed wide spread liver lesions suggestive of metastasis, small sclerotic lesion in the pelvis suggestive of bony metastasis, stable appearance of low volume mediastinal lymph nodes and abdominal lymphadenopathy. Her bone scan and myeloma results were reported normal. Her urine results showed raised urine creatinine ratio.Outcome of the Gastrointestinal Multidisciplinary team meeting was to offer liver biopsy to decide on palliative chemotherapy. However the histopathology report confirmed chronic granulomatous disease suggestive of sarcoidosis. Patient showed remarkable improvement on corticosteroid therapy. With the background history of malignancy and convincing radiological findings had undermined the clinical rationale of the possibility of sarcoidosis. This case further reinstates that sarcoidosis should be considered as a differential diagnosis in all clinical settings of hypercalcemia with suppressed parathyroid hormone. A histopathological diagnosis, if appropriate should be considered even in the absence of other classical features suggestive of sarcoidosis.

DOI: 10.1530/endoabs.65.P113

P114

Intermittent Hypercalcaemia in a Young Man

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A 33 year-old man was referred to the endocrine bone clinic following presentation with a 4 mm kidney stone and hypercalcaemia. Apart from mild fatigue, he had no other hypercalcaemic or concerning symptoms. He was not on any medications or supplements. He had a positive family history for kidney stones and reported that his grandmother had been noted to have hypercalcaemia in the past. There was significant consanguinity in his family. Examination was entirely normal while blood tests revealed intermittent hypercalcaemia between 2.50 and 2.83 mmol/l (2.2–2.6), with raised 24 h urinary calcium (7.8 mmol/24 h (2.5–7.5)). PTH was low at 0.3 pmol/l (1.6–7.2), with undetectable PTHrP (<1 pmol/l). 25OH-vitamin D was 83 nmol/l (70–150). Based on the concerning finding of hypercalcaemia with low PTH, cross-sectional imaging was performed which did not reveal any signs of malignancy or granulomatous disease. Therefore, further exploration of vitamin D metabolism was performed. This began with the finding of high-normal biologically active vitamin D ($1,25(OH)_2$-vitamin D 138 pmol/l (55–139)), and subsequent finding of a raised active:inactive ($1,25:24,25(OH)_2$-vitamin D ratio of 66 (7–30)). This suggested loss-of-function mutation in the CYP24A1 gene, which encodes the enzyme responsible for reducing activated vitamin D ($1,25(OH)_2$-vitaminD-24hydroxylase). Management included good fluid intake, low sun exposure, with low calcium

and vitamin D intake. With these measures, his latest calcium is 2.53 mmol/l with an intentionally low 25OH-Vitamin D of 33.4 nmol/l. This case illustrates a rare but important cause of intermittent hypercalcaemia. This patient had increased active $1,25(OH)_2$-vitamin D with low inactive $24,25(OH)_2$-vitamin D resulting in hypercalcaemia when presented with a significant dietary calcium load (hence intermittent). This case also demonstrates a rare but important differential in patients presenting with the otherwise highly concerning combination of hypercalcaemia and low PTH. He is shortly planning a family and so genetic counselling will be of paramount importance.

DOI: 10.1530/endoabs.65.P114

P115

Ventricular arrhythmia and cardiac arrest: a dramatic presentation of hypoparathyroidism

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Introduction
Cardiovascular manifestations of hypocalcaemia include reversible CHF, prolonged QTc and ventricular arrhythmias. In patients presenting with hypocalcaemia, diagnosis of hypoparathyroidism is straightforward, but determining its cause is challenging.
Case Report
33 year lady admitted (23 November 2018) with VF arrest. Bloods showed low calcium (1.62 mmol/l), magnesium (0.48 mmol/l) and potassium (2.3 mmol/l) and ECG showed prolonged QTc. PTH were inappropriately normal (2.4 pmol/l) and vitamin D low (34 nmol/l). Phosphate were normal (0.82 mmol/l) and eGFR >90. Parathyroid antibodies were negative. She had circumoral and finger tip paraesthesia/numbness in preceding two weeks. No evidence of gastrointestinal loss (diarrhoea, vomiting, PPI, coeliac disease, alcoholism or eating disorder) or renal loss (diuretics, recent AKI, abnormal urinalysis, or post-obstructive nephropathy). Menstrual cycles were regular. She was investigated earlier for iron deficiency anaemia with negative coeliac screen. No family history of electrolyte imbalance, sudden cardiac death, endocrine or autoimmune diseases. She was treated with intravenous magnesium and calcium. Potassium levels were normal except on arrival. Calcium and magnesium levels remained resistant to correction until alfacalcidol was started, within few days of which both levels were stabilised without supplementation. Levels on 31 May 2019: calcium 2.38 mmol/l and magnesium 0.7 mmol/l (on alfacalcidol 1 (g only). QTc prolongation occurs in hypocalcaemia, hypomagnesemia or hypokalemia. Arrhythmias occur when levels are significantly low (calcium <1.9 mmol/l, magnesium <0.4 mmol/l or potassium <2.5 mmol/l). In this case, hypocalcaemia might have caused VF arrest. Hypocalcaemia with high PTH occurs in vitamin D deficiency & CKD; hypocalcemia with low/low-normal PTH occurs in hypomagnesemia (PTH resistance) and hypoparathyroidism. With no history of neck surgery/irradiation/infiltrative/autoimmune diseases, a diagnosis of primary hypoparathyroidism is considered. Autoimmune hypoparathyroidism is still a possibility, as positive autoantibodies occur only in 25% of autoimmune hypoparathyroidism.
Conclusion
Most hypoparathyroidism patients present with paresthesia, cramps or tetany. However, rarely they can present with arrhythmias, seizures or bronchospasm/laryngospasm.

DOI: 10.1530/endoabs.65.P115

P116

Calcium imbalance in sarcoidosis and renal failure

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We describe a patient who was treated for hypercalcaemia with inadvertent ramifications. A 59 year old gentleman with a background history of chronic kidney disease stage (CKD) 4, type 2 diabetes mellitus, hypertension, congestive cardiac failure and bilateral lower limb below knee amputations, presented with hypercalcemia of 3.30 mmol/l (reference range 2.20–2.60) and suppressed PTH at 12 ng/l (reference range 15–65), from a previously raised PTH level of 162 due to CKD. Investigations showed raised ACE levels of 106 U/l (reference range 10–52), enlarged mediastinal and hilar lymph nodes on CT. A presumptive diagnosis of sarcoidosis was made in view of patient's reluctance to undergo invasive biopsy. He was treated with oral prednisolone 60 mg.od. Calcium normalised to 2.56 mmol/l within one week and continued to drop further leading to symptomatic hypocalcaemia at 1.87 mmol/l in 3 weeks. The PTH rose to 268 ng/l. This was treated with alfacalcidol and the calcium normalised. His was weaned off prednisolone and patient stopped alfacalcidol in few months and the calcium remains normal with a raised PTH.
Discussion
The likely explanation for the above findings is, renal 1-alpha-hydroxylase in the proximal tubule is inhibited in chronic kidney disease, leading to calcitriol deficiency. Extra renal 1-alpha-hydroxylase is upregulated in the sarcoid granulomas which produces calcitriol leading to hypercalcemia. On administering the prednisolone, the inhibition of calcitriol synthesis in macrophages, effectively leads to vitamin D deficiency induced hypocalcemia. The above presentation demonstrates the complex interactions between renal and extra renal 1-alpha-hydroxylases and their clinical significance. On performing a literature review, we were unable to any case report describing the above phenomenon. This case highlights the need for vigilance and close monitoring in treating hypercalcemia of sarcoidosis in the presence of preexisting renal disease.

DOI: 10.1530/endoabs.65.P116

P117

An unusual case of symptomatic hypercalcemia from Grave's Disease in a young Filipino female

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Hypercalcemia in hyperthyroidism is usually asymptomatic, and related to a concurrent primary hyperparathyroidism. In this report, we describe a case of symptomatic hypercalcemia secondary to Graves' disease alone.
Case report
A 24-year-old Filipino female presented to the emergency department with generalized weakness, vomiting and abdominal pain. No other symptoms were noted. She was otherwise previously healthy. Family history was unremarkable. During physical exam, she was noted to have a non tender palpable thyroid gland without bruit. Her ECG showed sinus tachycardia. The complete blood count and electrolytes were normal however, ionized calcium was high at 1.6 mmol/l (NV 1–1.3). Renal function was normal. Hydration with saline and Furosemide 20 mg once daily was started though calcium levels remained elevated. Other causes of hypercalcemia were excluded as PTH was appropriate suppressed (8.8 ng/l; NV 14–72), vitamin D was also suppressed (15.29 nmol/LNV: >30). CT scan of chest and abdomen and bone scan did not point to any underlying malignancy nor metabolic bone disease. Medication history was also unremarkable. She was hyperthyroid with a suppressed thyroid stimulating hormone level of 0.004 pmol/l (NV:0.55–4.78), free T3 of >20 pmol/l (NV:2.3–4.2), free T4 of 8.4 pmol/l (NV:0.89–1.76). Thyroid receptor antibody levels were raised at 41.07 (NV: < 1 kU/l) supporting the diagnosis of Graves'disease. She was started on propylthiouracil 50 mg four times daily, along with propranolol 40 mg three times daily. She was subsequently seen after two weeks with normal repeat calcium level and thyroid function test.
Conclusion
This report aims to highlight that thyroid disease should always be considered as a cause of hypercalcemia. It should be distinguished from concomitant primary hyperparathyroidism. The definitive treatment for the hypercalcemia is correction of thyroid function.

DOI: 10.1530/endoabs.65.P117

P118

Hypercalcaemia secondary to vitamin D deficiency in T.B patients

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A 45-year old lady admitted to hospital in October 2018 with generally unwell and nausea. She has a background of disseminated T.B. confirmed by EBUS with bronchoalveolar lavage in September 2018. She had previous CT thorax,

abdomen and pelvis in September 2018 which was reported as extensive lymphadenopathy with omental and peritoneal thickening. She also has a history of vitamin D deficiency in August 2018 at 7.1 nmol/l and was treated with oral colecalciferol. The biochemical results on admission showed adjusted calcium 4.22 (2:20–2:60 mmol/l), PTH 1.5 (1.6–6.9 pmol/l), Vitamin D 100.3 nmol/l, sodium 141 (133–146 mmol/l), potassium 4.7 (3.5–5.3 mmol/l), urea 4.2 (2.5–7.8 mmol/l), creatinine 61 (45–84 mmo/l), eGFR >90, ALT 19 (1–35 IU/l), ALP 150 (30–130 u/l), total protein 80 (60–80 g/l), albumin 37(34–48 g/l), bilirubin 6.0 (0–21 umol/l), phosphate 1.05 (0.8–1.5 mmol/l),
Historically, the biochemistry trends as per table below:
The patient was treated initially with intravenous saline 0.9% and received

Date 2018	28/08	19/09	24/10	25/10	26/10	28/10	29/10	30/10	31/10	01/11	02/11	13/11
Adjusted calcium	2.40	2.46	4.22	3.74	4.01	3.64	3.48	3.31	3.26	3.26	3.28	2.55
PTH			1.5									
Vitamin D	7.1		100.3									

subsequently zoledronic acid infusion for hypercalcaemia. She was previously started in community with oral colecalcifreol due to to severe vitamin D deficiency in August 2018 at 7.1 nmol/l which seems quite appropriately, treated her Vitamin D deficiency at that time. Unfortunately this extra colecalciferol has been subject to unregulated hydroxylation in her granulomatous tissue leading to the hypercalcaemia. The hypercalcemia thought to be secondary to high extra-renal production of 1,25 hydroxy vitamin D was seen in tuberculosis, including in individuals with 25 hydroxy vitamin D in the deficient range. These abnormalities of calcium metabolism are due to dysregulated production of 1,25 hydroxy vitamin D by activated macrophages trapped in pulmonary alveoli and granulomatous inflammation. Macrophage-derived 1α-hydroxylase as the source of the elevated 1,25 hydroxy vitamin D.

DOI: 10.1530/endoabs.65.P118

P119

Post thyroidectomy and parathyroidectomy: optimizing calcium monitoring and management

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Background
Postoperative hypocalcemia is common after extensive thyroid surgery and parathyroid surgery. There are various risk factors, although there is lot of variability.
Methods and results
The aim of this project was to examine and improve postoperative monitoring and management of serum calcium at a district general hospital. Process was mapped using a flow chart and was discussed in MDT to identify areas for improvement. Data was then collected to determine whether calcium was checked on day 1 post op, 2 weeks post-op, and 8 weeks postoperatively. Discharge letters were analyzed to determine whether patients were prescribed calcium and vitamin D as per protocol and whether patients were appropriately followed up. This was followed by interventions including making a protocol for monitoring, standardizing texts and electronic prescriptions for patients undergoing surgery, leading to improvement in management facilitating early discharge, reduction in risk of hypocalcemia, readmission and treatment related hypercalcemia. Normalization of calcium levels in majority of patients was observed at one week follow up, however, no significant predictor of early normalization or hypocalcemia post-surgery was found. The findings have been used to develop an agreed local post-operative hypocalcaemia management algorithm.
Conclusion
There is no single predictor of postoperative normalization of calcium levels or development of hypocalcemia and it should be checked at various intervals at locally agreed timeline.

DOI: 10.1530/endoabs.65.P119

P120

Persistent hypercalcemia in a patient with steroid sensitive sarcoidosis due to coexisting primary hyperparathyroidism

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Hypercalcemia is a relatively common extrapulmonary manifestation of sarcoidosis. Sarcoidosis-associated hypercalcemia is due to the uncontrolled synthesis of 1,25-dihydroxycholecalciferol and increased intestinal absorption of calcium which usually results in a low serum concertation of parathyroid hormone (PTH). High levels of PTH in patients with hypercalcemia secondary to sarcoidosis is usually an indication of co-existent primary hyperparathyroidism. We present a case of a 43-year-old white female with initial presentation of intermitted cough and shortness of breath. Chest X-ray revealed hilar lyphadenapathy which was suggestive of sarcoidosis. Serum angiotensin converting enzyme (ACE) was elevated at 91 ACEU. Sarcoidosis diagnosis was confirmed by excisional biopsy of the left cervical lymph node, histological examination showed numerous non-caseating granulomas. Other systemic involvement was not detected by further investigations. She had hypercalcemia with serum calcium 2.81 mmol/l and phosphate level of 0.81 mmol/l.Treatment with oral prednislone relieved her cough and dyspnea. However, her calcium remained high despite steroid therapy. A 24-h urine calcium and vitamin D level were normal. Her PTH noted to be elevated (range 6.9 and 11 pmol/l) in the presence of high calcium confirming coexisting primary hyperparathyroidism. Sestamibi parathyroid scintigraphy did not localize any parathyroid adenoma. She is arranged to undergo total parathyroidectomy with autotransplantation of one parathyroid gland in her forearm. This case highlights the importance of awareness of the possibility of coexisting primary hyperparathyroidism in patients with sarcoidosis.

DOI: 10.1530/endoabs.65.P120

P121

A case of proton pump inhibitor associated severe hypocalcaemia

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A 73-year-old man with a known history of Type 2 Diabetes, atrial fibrillation and hypertension presented with chest pain to the emergency department. His medication included metformin, bisoprolol, apixaban and omeprazole (long-term use). On clinical assessment, he complained of generalised aches and examination revealed bony tenderness over the chest wall. His electrocardiogram showed a prolonged QTc interval (495 ms). Biochemical tests revealed normal serum troponins, renal and liver function tests, an adjusted serum calcium of 1.43 mmol/l (2.20–2.60) and serum magnesium of 0.15 mmol/l (0.7–1.0). His corresponding serum parathyroid hormone level was 3.6 pmol/l (1.1–4.7). His serum total vitamin D level was 16 nmol/l (severely deficient). The patient was treated with intravenous calcium and magnesium infusions. Twelve hours later, when magnesium replete, his serum PTH was 15.4 pmol/l with a corresponding serum calcium of 1.89 mmol/l. Omeprazole (indication for long-term use unclear) was stopped without any recurrence of acid-reflux symptoms. Replacement doses of cholecalciferol (40 000 units weekly) and oral calcium were started. Prior to discharge from hospital, his serum calcium was 2.24 mmol/l and subsequent outpatient follow-up revealed maintenance of a normal serum calcium (without oral calcium supplementation), magnesium and vitamin D. This case illustrates important lessons. Proton pump inhibitor (PPI) treatment can cause severe hypomagnesaemia which can suppress PTH secretion and in the setting of vitamin D deficiency lead to severe hypocalcaemia. Indeed, in our patient, following replacement of magnesium, PTH levels rose appropriately to compensate for both hypovitaminosis D and hypocalcaemia. We propose that patients who require chronic PPI therapy should have regular monitoring of their calcium, vitamin D and magnesium levels. More importantly however, the indication for PPI use should be continually assessed.

DOI: 10.1530/endoabs.65.P121

P122

Differential diagnosis of pseudohypercalcaemia by measurement of ionised calcium

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Pseudohypercalcaemia is defined as an elevated total calcium level coincidental with a normal ionised calcium level. This rare phenomenon occurs in monoclonal gammopathy of unknown significance (MGUS). We report two cases of MGUS and a case of atopy with grossly elevated IgE levels exhibiting the phenomenon.
Case 1
31 year old female with MGUS, hypercalcaemia and normal parathyroid (PTH) levels. Parathyroid imaging normal. Consensus diagnosis of primary hyperparathyroidism. At surgery two apparently normal parathyroid glands removed but histology normal. Calcium and PTH levels unchanged but ionised calcium normal confirming pseudohypercalcaemia.
Case 2
74 year old male with MGUS, hypercalcaemia and normal PTH levels. Imaging normal. Diagnosed as primary hyperparathyroidism and surgery planned. The finding of a normal ionised calcium level avoided surgery.
Case 3
61 year old male diagnosed as having primary hyperparathyroidism on the basis of hypercalcaemia and normal PTH levels. Grossly elevated IgE levels and normal ionised calcium obviated imaging studies and surgical intervention. These cases demonstrate the utility of ionised calcium measurement in diagnosing pseudohypocalcaemia. We believe that this to be the first report of pseudohypercalcaemia due to high levels of a normal immunoglobulin.

DOI: 10.1530/endoabs.65.P122

P123

A case report of concomitant diagnosis of multiple myeloma and primary hyperparathyroidism

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Coexistence of primary hyperparathyroidism and multiple myeloma is very rare.
Case report
45 year old Jamaican female presented with left sided chest pain for a month. CXR showed a pathological left clavicular fracture with a lytic lesion. She was noted to have a serum Ca of 3.26 mmol/l.
Other investigations
Haemoglobin 115 g/l (115–155), creatinine 76 umol/l (49–92), Corrected Ca 3.26 mmol/l (2.20–2.60), Phosphate 0.60 mmol/l (0.87–1.45), PTH 16.8 pmolL (1.6–6.9), Vitamin D 26 nmol/l (Insufficient if 25–75); Paraprotein not detected, kappa light chains 44 mg/l (3.3–19.4 mg/l), lambda light chains 8.5 mg/l (5.7–26.3 mg/l), kappa lambda ratio 5.2 (0.26–1.65), urine-BJP negative and beta-2 microglobulin 4.3 mg/l (0.26–1.65), LDH 180 IU/l (135–214).
Bone marrow
80% plasma cells on trephine with findings consistent with high risk myeloma.
CT CAP
Expansile lytic lesion in left clavicle, probable pathological fracture of right fourth rib, multiple lytic lesions in bones and calculus in right kidney.
MRI spine showed an abnormal signal in multiple vertebrae.
US Neck
1.2 low density structure highly suspicious of enlarged parathyroid gland.
Parathyroid Sestamibi
Adenoma in the region of the upper pole of the left thyroid lobe. Patient was diagnosed with Oligo-secretory Myeloma, revised ISS stage two. She completed 6 cycles of chemotherapy and received monthly Zoledronic acid. She is awaiting stem cell transplant.
PET scan post-chemotherapy showed response to treatment with low-grade mild activity in left clavicle only. The patient was referred for Parathyroidectomy.
Discussion
Hypercalcemia as a presenting symptom of concomitant MM and Hyperparathyroidism is rare with 30 reported cases (Hussain *et al.* 2013). Majority were female with age ranging from 45 to 92 years. Our patient is the youngest to our knowledge. Parathyroidectomy, chemotherapy, and radiotherapy have been used for treatment with variable success. The prognosis has been generally poor with 28% dying within 5 years of diagnosis.

DOI: 10.1530/endoabs.65.P123

P124

The forgotten electrolyte-when hypercalcaemia presents with acute confusion

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61-year-old previously fit and healthy female presented with one-week history of confusion and altered consciousness. There was no history of fever, headache or limb weakness. She was dehydrated, Glasgow Coma Scale score was 11/15, pupils were equal and reactive to light bilaterally and rest of examination was unremarkable. Initial investigations are outlines in Table 1. X-ray-chest showed mediastinal lymphadenopathy and CT head was unremarkable. She was initially treated for sepsis and dehydration, but the clinical condition deteriorated over the next 48 h. Lumbar puncture and MRI brain performed after neurology consult which were unremarkable. Three days post admission; she also had bone profile, which showed very high calcium levels (5.86 mmol/l). Calcium had not been checked since admission. Further workup of hypercalcaemia is shown in Table 2. A CT chest/abdomen/pelvis showed bilateral hilar, mediastinal and abdominal lymphadenopathy. Bone marrow biopsy confirmed adult T-cell lymphoma on histology. She was treated with intravenous fluids, steroids initially and later commenced on chemotherapy with rapid improvement in her confusion and calcium levels.

Table 1

Investigation	Results	Reference range
C-Reactive Protein	6.1	1.50–1.72 mPA
Urea	25	2.5–7.8 mmol/l
Sodium	151	
TSH	1.3	0.4–5.33 miu/l
White cell count	18.6	3.8–10.8$\times 10^9$/l

Table 2

Investigation	Results	Reference range
Adjusted Calcium	5.83	2.2–2.6 mmol/l
Alkaline phosphatase	217	20–140 U/l
Parathyroid hormone	1.2	1.6–6.9 pmol/l
1,25(OH) vitamin D	39	20–120 pmol/l
Angiotensin converting enzyme	85	8–52 u/l

Conclusion
Hypercalcaemia is well-known to cause confusion and should be checked when other common causes of confusion are not present. Adult T-cell Lymphoma is a rare cause of calcitriol-mediated hypercalcaemia and responded well to steroids and cancer chemotherapy. Normal 1,25(OH) Vitamin D levels do not necessarily exclude granulomatous diseases in the investigation of non-Parathyroid hypercalcaemia.

DOI: 10.1530/endoabs.65.P124

P125

Symptomatic hypercalcemia from Graves' disease: a case report

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Hypercalcemia in hyperthyroidism is usually asymptomatic, and related to a concurrent primary hyperparathyroidism. In this report, we describe a case of symptomatic hypercalcemia secondary to Graves' disease alone.

Case report

A 24-year-old Filipino female presented to the emergency department with generalized weakness, vomiting and abdominal pain. No other symptoms were noted. She was otherwise previously healthy. Family history was unremarkable. During physical exam, she was noted to have a non tender palpable thyroid gland without bruit. Her ECG showed sinus tachycardia. The complete blood count and electrolytes were normal however, ionized calcium was high at 1.6 mmol/l (NV 1–1.3). Renal function was normal. Hydration with saline and Furosemide 20 mg once daily was started though calcium levels remained elevated. Other causes of hypercalcemia were excluded as PTH was appropriately suppressed (8.8 ng/l; NV 14–72), vitamin D was also suppressed (15.29 nmol/LNV: >30). CT scan of chest and abdomen and bone scan did not point to any underlying malignancy nor metabolic bone disease. Medication history was also unremarkable. She was hyperthyroid with a suppressed thyroid stimulating hormone level of 0.004 pmol/l (NV:0.55–4.78), free T3 of >20 pmol/l (NV:2.3–4.2), free T4 of 8.4 pmol/l (NV:0.89–1.76). Thyroid receptor antibody levels were raised at 41.07 (NV: < 1 kU/l) supporting the diagnosis of Graves'disease. She was started on propylthiouracil 50 mg four times daily, along with propranolol 40 mg three times daily. She was subsequently seen after two weeks with normal repeat calcium level and thyroid function test.

Conclusion

This report aims to highlight that thyroid disease should always be considered as a cause of hypercalcemia. A concomitant primary hyperparathyroidism should be ruled out. The definitive treatment for the hypercalcemia is correction of thyroid function.

DOI: 10.1530/endoabs.65.P125

P126

Hypocalcaemia presentation with HDR syndrome

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Introduction

HDR syndrome, is a rare, genetic syndrome characterized by hypoparathyroidism sensorineural deafness and renal disease. Mutations in GATA binding protein 3 (*GATA3*), a gene localized to the chromosome region 10p14-15, have been detected in families affected by the syndrome.

Case report

This is a 30 year old lady who was referred to the endocrine services with symptoms of generalized fatigue, mouth numbness and tingklining. Her past medical history include bilateral sensorineural deafness with hearing aids. In addition she has inborn unilateral renal agenesis. There was no previous history of calcium metabloism disorder. Her father had bilateral sensorineural deafness. Biochemical evaluation showed low calcium level, high phosphate level, low parathyroid hormone level and mild renal impairment. Providing her clinical presentation with hypocalcaemia, sensorinural deafness and renal impairment, HDR syndrome was suspected and genetic analysis was undertaken and showed mutations in GATA binding protein 3 (*GATA3*) which confirmed HDR syndrome.

Discussion

The HDR syndrome, also known as Barakat syndrome, is an autosomal dominant disorder caused by germline inactivating mutations of the GATA3 gene.1,2 GATA3 encodes a transcription factor that is involved in embryonic development of the parathyroid glands, inner ear and kidneys.3 The HDR syndrome has wide phenotypic variability. Hypoparathyroidism has a variable age of onset and is characterized by symptomatic or asymptomatic hypocalcaemia with undetectable or low serum PTH levels. Renal anomalies in HDR syndrome are also heterogeneous and include renal dysplasia, hypoplasia, or aplasia, and vesicoureteric reflux.

Conclusion

Diagnosis of HDR syndrome is still challenging, but clinicians should consider it in their differential diagnosis with a wide range of clinical manifestations including hypocalcemia, renal abnormalities and deafness.

DOI: 10.1530/endoabs.65.P126

P127

Severe hypercalcaemia and acute kidney Injury in a patient with sarcoidosis

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Introduction

Sarcoidosis is a multisystem granulomatous disorder. It commonly causes mild hypercalcemia in up to 10–20% of the cases and renal involvement can be a feature. Presentation with severe symptomatic hypercalcaemia (>3.5 mmol/l) and acute kidney injury is rare. We present an interesting case.

Case

A 58 year old female was referred to the emergency department by her general practitioner with a one month history of polyuria, generalised weakness and fatigue. She had a background of multisystem sarcoidosis with ophthalmic, pulmonary and lymphoreticular involvement diagnosed two years previously by tissue biopsy. Her sarcoidosis was in remission, with regular follow-up in respiratory clinic. She was off steroids for two years prior to admission. Her clinical examination was unremarkable.

Investigation and management

The laboratory results revealed an estimated glomerular filtration rate (eGFR) of 26 ml/min from a baseline of 67 ml/min a few months prior, high adjusted calcium (3.95 mmol/l), low vitamin D 25-OH (39 nmol/l, adequate >50 nmol/l), normal parathormone levels and a raised angiotensin converting enzyme of 109 U/l, all indicating active sarcoidosis. A diagnosis of severe hypercalcaemia and acute kidney injury secondary to an exacerbation of sarcoidosis was made. Renal ultrasound showed no evidence of stones or hydronephrosis; myeloma and immunology screening tests were negative. The patient responded to intravenous fluid resuscitation and 40 mg oral prednisolone, her calcium and renal function normalised and she was discharged with a reducing dose of prednisolone. Two months post-discharge serum calcium and eGFR remained normal on 5 mg prednisolone daily.

Discussion

We report a rare acute presentation of sarcoidosis, namely severe symptomatic hypercalcaemia and acute kidney injury. Early intervention in this case has prevented the long term sequelae of acute renal failure due to sarcoid related hypercalcemia.

DOI: 10.1530/endoabs.65.P127

P128

Unusual cause of hypophosphatemia in an adult

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The Fibroblast Growth Factor 23 (*FGF23*) gene provides instructions for making a protein called FGF23. This protein is necessary in regulating the phosphate levels within the body. We present a case of an adult Caucasian man with persistent hypophosphatemia due to mutation in ENPP1.

Case History

A 34 years old male presented with intermittent muscle pain, cramps and headaches. He also noticed episodic breathlessness and irritability. He had no history of diarrhoea and he was not on any medications. Blood tests showed persistently low phosphate and his 24 h urinary phosphate excretion was high. His calcium and PTH was normal. He had normal bone densitometry. He had no family history of any illness. He had a genetic test, found a pathogenic variant in the ENPP1 gene c.2375A>G p. (Asn792Ser). This variant has been reported before with other pathogenic variants in patients with hypophosphataemic rickets and infantile arterial calcification.

Discussion

Phosphate levels are controlled in large part by the kidneys. *FGF23* signals the kidneys to stop reabsorbing phosphate into the bloodstream. FGF23 also helps to determine the absorption of phosphate by the intestines and plays a role in regulating vitamin D. At least three mutations in the *FGF23* gene have been found to cause a rare form of hereditary hypophosphatemic rickets. This is described as autosomal dominant hypophosphatemic rickets (XLH). FGF23 loss-of-function mutations also causes familial hyperphosphatemic tumoral calcinosis (TC), The mutations cause overactivity of FGF23 resulting in decreased phosphate reabsorption by the kidneys, leading to hypophosphatemia. A combination of active vitamin D and phosphate salts is the current medical therapy. This therapy has certain efficacy and safety associated limitations. Several measures to inhibit

FGF23 activity have been considered as possible new treatments for FGF23-related hypophosphatemia. In particular, a humanized monoclonal antibody for FGF23 (Burosumab) is a promising treatment in these patients.

DOI: 10.1530/endoabs.65.P128

P129

Hyperparathyroidism in pregnancy – a missed opportunity in prenatal management?

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Hyperparathyroidism is rarely encountered in pregnancy; however, the consequence of untreated disease can be significant for both the mother and fetus (increased risk of miscarriage, IUGR, pre-eclampsia, neonatal hypocalcaemia). NICE guidance (May 2019) on the management of PHPT strongly recommends disease control pre-pregnancy, MDT working and offering surgery if cCa is above 2.85 mmol/l. We report a 31-year-old P4 who was referred to our joint endocrine/obstetric clinic at 12 weeks gestation with a history of hypercalcaemia. Two years prior she'd been found to have cCa of 2.7 mmol/l and PTH of 8.1 pmol/l, but unfortunately was lost to follow-up. Interestingly she'd had 2 early miscarriages since hypercalcaemia detection. She was counselled regarding the risks and advised to avoid dehydration, commence aspirin, undergo regular growth scans and have monthly calcium monitoring. She had negative genetic testing for FHH and PHPT was confirmed. She was asymptomatic and her cCa remained 2.66–2.76 mmol/l, until a few weeks pre-delivery when it rose to 2.85 mmol/l, so she was not referred for surgery. Her baby interestingly had raised, rather than expected reduced, calcium levels of 3.05 mmol/l and was treated with IV fluids and 'low' calcium formula combined with breast feeding. Postnatally the patient has increased renal stone load and is awaiting both urology and endocrine surgical input, her adjusted calcium fell to 2.62 mmol/l with a PTH of 7 pmol/l during breastfeeding.

Discussion

Antenatally our patient had cCa level <2.85 mmol/l, but it was highest just before delivery. It is thought that active placental transfer of calcium at this stage resulted in the raised level in her daughter. Unfortunately, several opportunities for prenatal counselling and treatment were missed and may have contributed to previous lower birthweight children, miscarriage history and hypercalcaemia seen in her daughter.

DOI: 10.1530/endoabs.65.P129

Endocrine Neoplasia and Endocrine Consequences of Living with and Beyond Cancer

P130

Nuclear receptor profiling predicts chemical disruptors as risk factors for developing breast cancer

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Triple negative breast cancer (TNBC) represents 10–20% of all breast cancers diagnosed, affects young people and is highly aggressive. These tumours lack expression of the receptors that bind estrogen and progesterone and stratify patients for hormonal therapy. The only current therapeutic option for TNBC is chemotherapy which has limited efficacy, and therefore novel therapies are desperately needed. The receptors for estrogen and progesterone belong to the nuclear receptor (NR) superfamily of ligand activated transcription factors. This family comprises 48 receptors which respond to metabolic, reproductive and immune cues. The entire gene set controlled by an individual NR is very specific, but we now realise that groups of NRs control overlapping gene sets, suggesting functional redundancy. NRs therefore work together to regulate key physiological processes, enabling fine tuning and subtle control of essential metabolic, reproductive and immune functions. This suggests that in estrogen receptor (ER) and progesterone receptor (PR) negative breast cancers that other NRs might be important in disease development/progression – and therefore represent tractable therapeutic targets. We have profiled the entire NR superfamily (48 receptors) in 168 breast cancer samples to identify other NRs with altered expression, and in parallel compared NR expression with patient outcome in a larger cohort to link to underlying pathology. We show that a large proportion of the NR superfamily have altered expression in breast cancer, and that 20 of the 48 NRs have altered expression in TNBC compared with normal tissues. The expression of 8 of these were also associated with shorter patient survival times. Using Enrichr software, we identify chemical disruptors – household detergents, antiseptics, industrial pollutants and prescribed medications – predicted to either activate these NRs, or alter their expression. These not only represent risk factors underlying dysregulation of NR function responsible for developing TNBC, but also highlight points for therapeutic intervention.

DOI: 10.1530/endoabs.65.P130

P131

Inflammatory cytokines dysregulate oestrogen metabolism in colorectal cancer

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Colorectal cancer (CRC) is the third most common cancer and is one of the highest incidences and mortality tumours worldwide. Our group has previously shown that CRC favours oestradiol synthesis by increasing steroid sulfatase (STS) activity and altering 17β-hydroxysteroid dehydrogenases (HSD17Bs) expression. However, what regulates STS activity and HSD17Bs expression and activity in CRC remains unknown. In breast and prostate cancer inflammatory mediators, such as TNFα, increase STS activity. Therefore, we hypothesised that specific inflammatory cytokines may regulate STS activity and HSD17Bs expression in CRC. To examine this, we tested the effect of TNFα, IL-6, IL-4 and Interferon gamma (IFN-γ) on STS activity, HSD17Bs expression and activity (HSD17B1, HSD17B2, HSD17B4, HSD17B7, HSD17B12), and oestrogen receptor (ERα, ERβ, and GPER) expression in various colon adenoma (R9/C2/51) and CRC cell lines (HCT116, Colo205, LoVo). We also calculated correlation coefficients between these inflammatory cytokines and HSD17Bs and oestrogen receptors expression in the human colon adenocarcinoma (COAD) RNA-Seq dataset ($n=440$) from The Cancer Genome Atlas (TCGA). TNFα, but not IL-6, IL-4, or IFN-γ, significantly ($P<0.001$) increased STS activity in CRC cells. TNFα treatment (at 10, 20 and 40 ng/ml for 24 h) also significantly downregulated HSD17B2 expression, whilst increasing the expression of HSD17B7. TNFα had no effect on HSD17B7 or HSD17B12 expression. All other cytokines tested had no effect on HSD17Bs expression or activity. Interrogation of the TCGA COAD dataset also identified positive correlation between TNFα and HSD17Bs supporting our results in cell lines. These novel findings demonstrate that in CRC TNFα increases pathways that favour oestradiol synthesis and thus acts as a potential pro-proliferative mechanism. Coupled with our previous findings that TNFα can increase oestrogen uptake pathways, this data suggests TNFα is the key regulator of oestrogen metabolism in CRC.

DOI: 10.1530/endoabs.65.P131

P132

Risk stratification of variants of unknown significance (VUS) in monogenic endocrine tumour genes using population-level genetic data and computational analysis

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Background

Identifying individuals harbouring germline mutations in hereditary cancer genes provides opportunities for tumour surveillance programs, disease-specific treatment and cascade testing in family members but is reliant on accurate variant interpretation, which may be confounded by imprecise methods for ascribing pathogenicity. Where insufficient evidence supports a definitive classification, 'variant of uncertain significance' (VUS) status is applied, which

often leads to clinical uncertainty. Here, population-level genetic data and high-throughput computational tools were employed to aid VUS stratification relevant to monogenic endocrine tumour syndromes.
Methods
Thirteen genes were selected and all rare (allele frequency $<0.05\%$) non-synonymous single nucleotide variants (SNVs) occurring in the GnomAD non-cancer cohort identified ($n=134$, 187 individuals). Variants were evaluated using the CharGer bioinformatic pipeline, which applies individual ACMG variant interpretation criteria into a single score, facilitating classification into benign, VUS, or pathogenic categories. Variant pathogenicity scores were derived using the ensemble prediction tool REVEL and gene-specific violin plots generated. These were compared to the distribution of REVEL scores for all possible missense SNVs for each gene as well as known pathogenic missense SNVs reported in mutation databases.
Results
High cumulative frequencies of rare missense SNVs were observed in the GnomAD control cohort for each of the 13 genes, with the great majority allocated VUS status by ACMG criteria. REVEL pathogenicity prediction scores for these variants revealed gene-specific distributions. Notably, for the majority of genes (e.g. *MEN1, NF1, RET*), the control population variants demonstrated negative selection against the most pathogenic REVEL scores, whilst distributions for known pathogenic variants were markedly skewed towards higher scores.
Conclusions
Gene-specific metrics encompassing the cumulative frequency of VUS variants in the background population, together with CharGer and REVEL scores can enhance the risk stratification of SNVs allocated VUS status during genetic testing. This information may be used to develop gene-specific thresholds to guide clinical management.

DOI: 10.1530/endoabs.65.P132

P133

Tumour detection and outcomes of surveillance screening in *SDHB* and *SDHD* mutation carriers

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Background
Pathogenic variants in genes encoding Succinate Dehydrogenase subunits B and D (*SDHB/SDHD*) predispose to Phaeochromocytoma and Paraganglioma (PPGL). Cascade genetic screening identifies relatives at risk and allows surveillance screening to enable early detection of PPGLs.
Methods
Retrospective analysis of genetic databases and hospital records between January 2000 and December 2018 identified relatives carrying *SDHB* and *SDHD* pathogenic variants. Surveillance screening included annual plasma metanephrine measurements and whole-body MRI with contrast every 3–5 years. 53 *SDHB* patients and 10 *SDHD* patients with no prior history of PPGL underwent surveillance screening. The median age at first screen was 34.5 years (range 8–74), with a median screening duration of 3 years (range 1–15).
Results
In *SDHB* group, PPGLs were detected in 9 (17%) non-index cases, of which 44% were sympathetic PGLs, 44% head/neck PGLs and 12% PCC. The youngest diagnosed with PPGL was aged 20 years. 89% of tumours were detected by MRI, while only 1 (11%) was detected following elevated plasma normetadrenaline level and interval functional imaging. No multifocal or metastatic disease was detected. In *SDHD* group, 6 (60%) of patients were diagnosed with PPGL at initial screening. 33% patients were diagnosed with multifocal disease, 50% of tumours located in the head/neck, and 50% along the sympathetic chain. All tumours were visualised on MRI, with 2 sympathetic PGLs also having raised normetanephrine levels. Penetrance of PPGL in non-index cases at age 50 and 70 respectively were 16.0% and 52% in *SDHB* and 72% and 82% in *SDHD*.
Conclusion
Screening enabled the detection of PPGLs in 24% of carriers at first screen of family members affected by either *SDHB* or *SDHD* mutations, with *SDHD* associated with higher incidence of multifocal disease. Penetrance estimates, similar to literature, demonstrated that tumour burden continues with age therefore confirming the need for lifelong screening.

DOI: 10.1530/endoabs.65.P133

P134

PLK1 inhibitors as potential new treatment for adrenocortical carcinoma

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Background
Adrenocortical carcinoma (ACC) is a rare aggressive cancer with limited treatment options for advanced stages. By targeted RNA expression screening, we identified polo-like kinase 1 (PLK1) as one of most overexpressed genes, thus representing a potential drug target for ACC. PLK1 inhibitors are under evaluation in clinical trials for other solid cancers and seem to be more effective in TP53 mutated tumours. The aim of the study was to evaluate PLK1 protein levels in a large series of ACC and test the efficacy of PLK1 inhibitors by functional experiments.
Methods
A total of 104 formalin-fixed paraffin-embedded tissue samples from ACC patients with available clinical and genetic data at tumour level were investigated. Nuclear PLK1 protein expression was evaluated by immunohistochemistry (anti-mouse monoclonal PLK1 antibody) and semi-quantitative H-score. Efficacy of PLK1-specific inhibitor Volasertib was tested in the standard NCI-H295R ACC cell line, which presents PLK-1 overexpression and TP53 deletion of exon 8 and 9, using different concentrations (50–200 nM) and time points (0, 48, 72 and 96 h). Cell proliferation was analysed using CyQUANT (Invitrogen).
Results
Nuclear PLK1 expression was classified as high in 59% of ACC samples, being more frequently elevated in TP53-mutated ($n=24$) than in TP53 wild type cases ($n=80$, 87.5 vs. 51%, $P<0.01$). No relationship was observed between PLK1 levels and either progression-free or overall survival. We found a concentration-dependent reduction of cell viability with *in vitro* dose response analysis, with a significant decrease in cell proliferation starting at 100 nM Volasertib treatment, compared to the vehicle control.
Conclusion
In this pilot study, we propose PLK1 inhibitors as promising candidates for treatment of a subset of ACC patients that may be pre-selected according to the tumour molecular pattern. We plan to extend functional experiments to further PLK1 inhibitors and further ACC cell lines with a different molecular profile.

DOI: 10.1530/endoabs.65.P134

P135

The impact of gastrointestinal symptoms on quality of life in people with MEN2B

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Introduction
Besides medullary thyroid carcinoma and other endocrinopathies, people with MEN 2B have intestinal ganglioneuromatosis. A recent MEN2B cohort study reported high rates of gastrointestinal (GI) symptoms: we hypothesized these might have a major impact on patients' daily lives.
Methods
An online survey was conducted among patients from Association for Multiple Endocrine Neoplasia Disorders (AMEND). This incorporated relevant elements from clinical history plus 2 well-validated questionnaires: SAGIS assessment of GI symptoms on quality of life; PAC-QoL for the impact of constipation on daily activities.
Results
There were 85 respondents, MEN2B ($n=28$), MEN2A ($n=57$). In MEN2B, 85% reported two or more GI symptoms. Epigastric pain was reported by 92% ($n=26$), with 50% ($n=14$) scoring >7/28 in the SAGIS epigastric pain domain. Abdominal cramps were a problem for 71.4% ($n=10$) and half of these described cramps as very severe. Difficulties with swallowing affected 43% ($n=12$). Diarrhoea affected 82.1% ($n=23$), of whom half ($n=11$) had high calcitonin levels. There was a trend for higher SAGIS scores in MEN2B than MEN2A (not statistically significant in our small cohort). In MEN2B, constipation was a major problem, reported by 75% ($n=21$) with 38.8% ($n=7$) of these reporting a SAGIS score >10/12 in the constipation domain. In contrast, in MEN2A group, only one

person (2.3%) scored >10/12. The effect of constipation on quality of life is severe in MEN2B; as measured by PAC-QOL. All patients reported dissatisfaction with their current treatment for constipation.

Conclusions

We report unmet needs of patients with MEN2B syndrome. The GI symptoms, especially constipation, had a severe impact on the quality of life in people with MEN2B. This suggests that there is room for improvement in the quality of care offered for these patients.

DOI: 10.1530/endoabs.65.P135

P136

Profiling of tissue inflammatory cytokine expression in a pancreatic neuroendocrine tumour mouse model identifies upregulation of the chemokine C-C motif ligand 2 (CCL2)

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Pancreatic neuroendocrine tumours (PNETs) may occur as part of the multiple endocrine neoplasia type 1 (MEN1) syndrome, or as a non-familial isolated endocrinopathy. Current medical treatments for PNETs are largely ineffective in preventing tumour progression, so there is a need for better therapies, which will develop from an improved understanding of the mechanisms driving PNET tumorigenesis. Cytokine-driven inflammation has been implicated in the development and progression of various cancers, such as breast, colorectal and lung cancer; however, little is known about the role of inflammatory mediators in PNETs. We therefore analysed the pancreatic expression of 40 inflammatory cytokines in a conditional *Men1* knockout mouse model, *Men1*$^{L/L}$*/RIP2-Cre*, in which PNETs of the β cells develop by 6 months of age. All animal work was performed under an approved UK Home Office licence. Whole (tumour-laden) pancreas protein extracts were isolated from female ($n = 5$) mice aged between 7–10 months of age, and were interrogated with inflammation antibody arrays, consisting of 40 known murine inflammatory factors. Signal intensity values were compared with those of pancreata harvested from wild type female ($n = 5$) control mice. Of 40 potential candidates, only one chemokine, C-C motif ligand 2 (CCL2), was significantly upregulated in the pancreata of *Men1*$^{L/L}$*/RIP2-Cre* mice (100% increase $P < 0.001$), when compared to wild type mice. CCL2 (also known as monocyte chemoattractant protein-1, or MCP-1) is a potent chemokine involved in recruiting monocytes and macrophages to sites of inflammation via activation. CCL2 has also been shown to play a role in angiogenesis, proliferation and metastasis in various solid organ malignancies. Thus, our data suggests the possible role of CCL2 in the pathogenesis of PNETs and as a novel therapeutic target for these tumours.

DOI: 10.1530/endoabs.65.P136

P137

Long term outcomes following parathyroidectomy in patients with multiple endocrine neoplasia type 1: A retrospective cohort study

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Primary hyperparathyroidism (PHP), usually due to multigland hyperplasia, occurs in >90% of patients with multiple endocrine neoplasia type 1 (MEN1). The literature is divided on the optimal surgical management for such patients. We report a retrospective cohort study on the long-term outcomes associated with limited, subtotal, or total parathyroidectomy as initial surgery for PHP in MEN1. The primary endpoint was recurrent PHP defined as an adjusted serum calcium >2.6 mmol/l with elevated or normal serum PTH. Kaplan–Meier curves were constructed for the primary endpoint. Rates of permanent post-surgical hypoparathyroidism (PPSH) were observed, and between group differences were assessed using Fisher's exact test. 51 MEN1 subjects, with median post-surgical follow-up of 11.8 years (IQR 7.2–17.6), were included and divided into 3 groups based on the number of glands removed at initial surgery; limited (<3 glands, $n = 26$), subtotal (3/3.5 glands, $n = 16$), and total (4 glands, $n = 9$). The proportions of patients with recurrent PHP at last follow-up were 17/26 (65.4%), 11/16 (68.8%) and 3/9 (33.3%) respectively. Median (95% CI) recurrence-free survival was 4.6 (1.0–6.8), 9.8 (2.5–30.4) and 30.5 (2.0-undefined) years, respectively. Compared to limited parathyroidectomy, both total and subtotal parathyroidectomy were associated with longer recurrence-free survival ($P = 0.001$ and $P = 0.016$, respectively), with no difference seen between total and subtotal parathyroidectomy ($P = 0.4$). Rates of PPSH were higher in the total parathyroidectomy group (5/9, 55.6%) compared to both limited (2/26, 7.7%, $P = 0.006$) and subtotal groups (1/16, 6.3%, $P = 0.012$). We conclude that, compared to both total and subtotal parathyroidectomy, limited parathyroidectomy is associated with a greater likelihood of recurrent PHP. Conversely, compared to both limited and subtotal parathyroidectomy, total parathyroidectomy is associated with higher rates of PPSH. Based on our data, subtotal parathyroidectomy may thus be the optimal strategy to balance these outcomes.

DOI: 10.1530/endoabs.65.P137

P138

Targeting oestrogen synthesis and action as a novel therapy for colorectal cancer

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Colorectal cancers (CRC) represent 9.4% of all cancers, with about 42 000 new UK cases per year. Current treatment involves surgical resection followed by radio- and chemo-therapy. 5-Fluorouracil is the standard post-operative chemotherapy although tolerance is poor due to dose-limiting toxicities and drug-resistance. **New treatment strategies are therefore sorely needed.** One emerging chemotherapeutic option is to target oestrogen metabolism. Our novel work reveals synthesis of biologically active oestradiol (E_2) is up-regulated in CRC tissue, with this correlated with increased CRC growth. Our data suggests that 17β-hydroxysteroid dehydrogenase type-7 (HSD17B7) is the enzyme primarily responsible for the conversion of oestrone (E1) to E2 in CRC. However, little is known about the regulation of HSD17B7 and whether inhibiting its action in CRC can block E2 synthesis. Here using LC–MS/MS methods and in various CRC cell lines (HCT116, HT-29, LoVo, SW620), we investigated whether these cells can all convert E1 to E2. We have also examined if starving the cells of oestrogens and then replacing oestrogen (E1 or E2) concentrations can regulate HSD17B7 expression. We have also synthesised HSD17B7 inhibitors that have been used to block E1 to E2 conversion in CRC cell lines. CRC cell lines, apart from HT-29, synthesised E1 to E2 with a greater conversion rate when compared to E2 to E1 synthesis. This suggests that CRC favours E2 synthesis. Oestrogen starvation of the CRC cells resulted in a significant increase in HSD17B7 expression. Replacement of oestrogens did not decrease HSD17B7 expression to control levels. HSD17B7 inhibitors significantly ($P < 0.01$) reduced E2 synthesis when CRC cells were treated with E1. These data suggest that low oestrogen concentrations can increase HSD17B7 expression and activity in CRC. Furthermore, we demonstrate that inhibition of HSD17B7 can reduce E2 synthesis in CRC and this may be a new treatment option for this malignancy.

DOI: 10.1530/endoabs.65.P138

P139

Clinical spectrum of endocrine toxicities of Immune checkpoint therapy: single centre experience

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Introduction

Checkpoint inhibitor (CPI) related endocrine toxicities are increasingly commonly with the use of these new cancer agents. With one of the largest cancer departments in UK, we studied the clinical management and outcome of patients who developed different endocrine toxicities over the last five years, with the use of CTLA-4, PD-1 and PDL-1 agents.

Methods
All patients treated with CPI between 1 Jan 2014 to 31 Jan 2019 were included for the retrospective analysis. Cases with pre-existing endocrine diagnosis and abnormal baseline results were excluded from the analysis (104/460 patients).
Results
Out of the 356 patients treated with CPI, 87 patients (24.4%) developed endocrine toxicities. Of these 87 cases, 8 patients (9%) were treated with CTLA-4, 65 with PD-1 (74%), 11 (12%) with combination of CTLA-4 and PD-1; and 3 cases were treated PDL1. A total of 70 cases (19.6%) were found to have thyroid dysfunction, 15 (4.2%) with hypophysitis and 2 cases with Type 1 DM. 7 patients having dual pathologies. Thyroid dysfunction was the most common toxicity in PD1 treated cases (64 patients out of 269 treated: 24%). 22 patients developed permanent hypothyroidism. Recovery for thyroid dysfunction was variable (18%: Pembrolizumab; 33%: Nivolumab). Isolated ACTH deficiency was the most common pituitary abnormality (11/15) in patients diagnosed with hypophysitis. 76 patients (87.3%) had relatively mild toxicities (CTCAE grade <3), while 11 patients (13%) required hospitalisations (CTCAE ≥ 3). 31 patients were asymptomatic on diagnosis.
Conclusion
CPI related endocrine toxicity occurred in 25% patients with thyroid dysfunction, followed by hypophysitis. 35% patients were asymptomatic and identified by blood testing. In the majority of cases the ICT could be safely continued. Surveillance protocols are required to allow safe use of ICT, and can help identify and manage adverse effects whilst facilitating uninterrupted use of immunotherapy.

DOI: 10.1530/endoabs.65.P139

P140

A cyclin dependent kinase inhibitor 1B missense mutation (Pro69Leu) is associated with familial hypomagnesaemia, but not multiple endocrine neoplasia type 4 (MEN4)

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Mutations in cyclin dependent kinase inhibitor 1B (*CDKN1B*) are associated with multiple endocrine neoplasia type 4 (MEN4), in which patients typically develop parathyroid and anterior pituitary tumours, and occasionally tumours of the pancreas, adrenals, kidneys and reproductive organs. Here, we report a family with a missense mutation of *CDKN1B* (p.Pro69Leu) that did not have MEN4-associated tumours, but instead had hypomagnesaemia. The proband, presented with fatigue, cramps, thirst, hypomagnesaemia, and Hashimoto's thyroiditis, and subsequently also developed uterine fibromas and episodic frontal alopecia. The proband, mother and stepsister had hypomagnesaemia, due to renal magnesium wasting, and Hashimoto's thyroiditis; but none of them had primary hyperparathyroidism, pituitary tumours, pancreatic neuroendocrine tumours or phaeochromocytoma; a maternal aunt had Hashimoto's thyroiditis only. Hypomagnesaemia, which occurs in ~30% of hospitalised patients, can result from gastrointestinal and renal loss, and may also occur as: part of a hereditary syndromic disorder (e.g. autosomal dominant hypocalcaemia or Bartter syndrome type V); or an isolated non-syndromic familial disease. Owing to the large number of genes encoding transporter proteins involved in magnesium homeostasis that could be responsible, whole exome sequencing was undertaken in the three family members with hypomagnesaemia after obtaining informed consent. No mutations were identified in known magnesiotropic genes, but a heterozygous c.206C>T *CDKN1B* variant, that predicted a missense mutation p.Pro69Leu of an evolutionarily conserved amino acid, was identified. The *CDKN1B* Pro69Leu mutation co-segregated with hypomagnesaemia, but not Hashimoto's thyroiditis, among six family members (three with renal magnesium wasting and Hashimoto's thyroiditis, one with Hashimoto's thyroiditis only, and two unaffected members). The Pro69Leu missense *CDKN1B* mutation, which has been previously reported in MEN4 patients, results in rapid proteosomal degradation and reduced binding to cyclin dependent kinase 2 (CDK2). Thus, our studies expand the spectrum of clinical features associated with *CDKN1B* mutations, to include renal magnesium wasting.

DOI: 10.1530/endoabs.65.P140

P141

Predicting hypophysitis in patients treated with immune checkpoint inhibitors: can prolactin be used as a marker of incipient disease?

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Background
Immune checkpoint inhibitors (ICIs), approved in the UK for the treatment of increasingly numerous malignancies, are commonly associated with endocrine sequelae, some of which may be life threatening. Society for Endocrinology guidelines detail management protocols for acute endocrinopathies, however widely accepted standards for their routine detection are lacking. Hypophysitis, clinically and radiologically silent in many, is seen in up to 15% of patients on ICIs and may result in potentially serious hormonal or mass-related complications. Prolactin is an easily measurable, inexpensive, glucocorticoid-independent anterior pituitary hormone which can be abnormal in early pituitary dysfunction.
Hypothesis
Low prolactin in patients on ICIs may predict incipient hypophysitis.
Methods
Retrospective review of all patients referred to joint endocrinology/oncology ICI clinic between January 2018 and May 2019. Prolactin nadir in patients on ICI therapy with subsequent, unequivocal secondary adrenal insufficiency ($n=16$) compared against control group of prolactin nadir in patients on ICI therapy without hypophysitis ($n=32$).
Results
Using a cut off of <115 mu/l, a low prolactin had a 93.75% specificity (95% confidence intervals 79.2–99.2%) and 50% sensitivity (95% confidence intervals 24.7–75.3%) for predicting hypophysitis in patients on ICIs. The Mann–Whitney *U* test demonstrated that the median prolactin was significantly lower in those patients who went on to develop hypophysitis than their matched controls ($P = 0.0027$).
Conclusions
A nadir prolactin of <115 mu/l is a highly specific but poorly sensitive marker for emergent hypophysitis. Given its low cost and widespread availability, serial measurements could be easily included in patients' oncological surveillance blood tests. Those patients with prolactin levels below our proposed cut off should be identified for more intensive monitoring and investigation, with a high degree of suspicion for early hypophysitis. Such measures could prevent emergency hospital admissions when consequent cortisol deficiency becomes acutely manifest.

DOI: 10.1530/endoabs.65.P141

P142

Living with and beyond childhood cancer – endocrine impact up to 40 years on

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Objective
To review impact of childhood cancer treatment on endocrine, gonadal and thyroid function.
Methods
Retrospective review of electronic records of 79 females, 90 males over 6 months of clinic visits from a Late Effects of childhood cancer clinic. Age at diagnosis: 8.5 years (range 5 months–9 years); time from treatment 23.5 years (range 10–40). Diagnoses: ALL, AML, Hodgkin's lymphoma, Non-Hodgkin's lymphoma, sarcomas, Wilms, Neuroblastoma, Primitive neuroectodermal tumour. Treatment regimens: chemotherapy (CHT), cranial radiotherapy (RT), total body irradiation (TBI) testicular, lung, regional RT, haemopoetic stem cell transplant (HCST). Endocrine, reproductive function, thyroid status, thyroid cancer, multinodular goitre (MNG) were noted.
Results
Females
56/79 women had regular periods, 30/79 became pregnant. 15/79 had POI. 7/90 had other pregnancy risks (uterine RT/anthracycline exposure). For oestrogen replacement in POI: 12 HRT, 3 OCP and one, none.
Males
14/90 men documented as having children. 15/90 had testicular failure, 12 on testosterone. 15/90 had azoospermia including 6 having endocrine testicular failure on replacement (TBI or cranial/testicular RT and alkylating agents). 44/90 reproductive status was undocumented.

Thyroid
4/169 patients had MNG; 1 follicular thyroid cancer, none of whom had neck RT. 20/169 diagnosed hypothyroidism. None had documented TSH >10 mIU/l. 9/20 had RT involving the thyroid. GH was the commonest hormone deficiency and ACTH the least common.
Discussion
There is a differential effect of CHT and RT treatment in men: CHT affects sertoli cell function, whereas heavily treated men (RT and CHT) are azoospermic requiring testosterone replacement. As well as issues conceiving, pregnancy can be high risk. Young women with POI are taking more HRT contrary to suggestion that it's use may be stigmatised. Thyroid status is uncertain with a low threshold for starting thyroxine. These young adults have complex and multiple health needs. As this patient group increases in number we need to develop services accordingly.
DOI: 10.1530/endoabs.65.P142

P143

Ipilimumab-induced hypophysitis: a longitudinal analysis in a cohort of patients with metastatic melanoma
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Introduction
Ipilimumab is a human monoclonal antibody directed against cytotoxic T-lymphocyte antigen-4 (CTLA-4) that has been shown to significantly improve survival in patients with metastatic melanoma. Immune-related adverse events (irAEs) occur in some patients with increased T-cell activation, of which ipilimumab-related hypophysitis (IH) is an important treatment complication. The aim of this study is to determine the incidence of IH and characterise clinical presentation and outcomes in these patients.
Patients and methods
We retrospectively evaluated adult patients with melanoma treated between December 2010 and April 2018 at a tertiary referral centre. All patients received ipilimumab (3 mg/kg) monotherapy or in combination with nivolumab. Symptoms, pituitary hormone assessment, pituitary imaging and patient survival were assessed.
Results
Of 120 patients treated with ipilimumab, 11 patients (55% male; age at onset 60.8 ± 8.5 years) presented with hypophysitis. The median onset was at 16.4 weeks (range: 8.4–64.6 weeks) after treatment start, occurring in 73% after the fourth infusion. The main presenting symptom was lethargy ($n=8$) followed by headache ($n=5$). All patients had ACTH deficiency. A fall in TSH prior to cortisol was observed in six patients at a median duration of 10.6 weeks (range: 8.8–19.2 weeks) after commencing ipilimumab and a median of 3.7 weeks (range: 2.8–10.1 weeks) before the diagnosis of hypophysitis. Gonadotroph deficiency was detected in two patients. By end of follow-up (median 16.7 months, range: 2.8–58.4 months), corticotroph deficiency was persistent in all patients; all but one patient recovered thyrotroph function and gonadotroph deficit completely recovered. Additional irAEs were diagnosed in five patients with IH, including one case of autoimmune diabetes. Three patients with hypophysitis died within the first year of immunotherapy.
Conclusion
The incidence of IH was 9.2%, predominantly occurring after the fourth infusion. Usually, hormonal deficits improved, except for corticotroph function. TSH fall may be an early predictor of IH.
DOI: 10.1530/endoabs.65.P143

P144

The yield and cost of radiological screening in von Hippel–Lindau disease
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Introduction
Patients with the familial cancer syndrome von Hippel–Lindau disease (VHL) are enrolled in radiological screening programmes which aim to identify tumour development at an early stage. This facilitates timely intervention to lesions when the risk of metastatic spread is low and when they are conducive to less-invasive and parenchymal-sparing interventions, thereby minimising treatment-related morbidity. A number of international screening protocols exist, although there has been limited evaluation of their outcomes particularly with regard to their yield and cost.
Methods
Retrospective review of the case records of patients with VHL (based on positive genetic analysis or fulfilment of the clinical criteria for diagnosis) cared for at St Bartholomew's Hospital, London. An adapted version of the VHL Alliance guidelines were used to guide minimum screening frequency with techniques that minimise ionising radiation exposure being preferentially employed.
Results
Thirty-three patients (20 male, 13 female) were included in the analysis. Median follow up duration was 12.3 years. Across the cohort, the crude rates of interventions per scan were 6.25%, 2.42% and 9.83% for cerebral, spinal and abdominal imaging respectively. This equates to a 'number needed to scan' for one intervention of 16, 41 and 10 in each body area. Using the 2019/20 National Tariff Payment System, the associated imaging costs for each intervention were approximately £2770 for cerebral pathology, £7938 for spinal and £1437 for abdominal. For each body site, surveillance imaging did not result in intervention in 66.7%, 90.9% and 42.4% of patients during the examined follow up period.
Discussion
A significant proportion of scans performed according to international guidelines for radiological screening in VHL do not result in intervention. This raises the question as to whether less intensive surveillance might be possible, particularly for spinal disease, in which indications for intervention are largely based on symptomatology rather than scan appearance.
DOI: 10.1530/endoabs.65.P144

P145

DI patients vote for a name change to pituitary insipidus to improve safety – a survey
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Aims
To discover the views of patients with Diabetes Insipidus (DI) on difficulties they encounter with managing DI in different circumstances; the possible causes of these difficulties and how these might be improved for their safety.
Background
Between 2009 and 2015 there were 471 serious adverse inpatient incidents and 2 deaths involving DDAVP administration[1]. The analysis of one death resulted in a suggestion that the name of the condition was a contributory factor[2].
Method
At the National Pituitary Foundation patient's conference in April 2019, a questionnaire entitled 'Living with Diabetes Insipidus' was distributed to any DI patients who requested it.
Results
22 completed questionnaires from patients with DI were returned. Mean age was 54 years (17–73). Mean duration of DI was 35.7 (2–69). The majority (59.1%) considered the worst situation for them was in hospital casualty or as an inpatient. 90.9% thought the main difficulty was confusion with Diabetes Mellitus (DM). 100% thought a name change would help them. The most popular choice of a new name was Pituitary Insipidus (PI) 16/22 (72.7%). Negative comments were made against the other choices. An emergency card and improved staff education were also voted for. There were no votes for leaving the current situation unchanged.
Conclusions
Patients' primary wish is to rename DI with PI to improve their safety. There are 2 reasons for this name change: 1. It takes away the word 'Diabetes' which continues to cause confusion and deaths. 2. By including the word 'Pituitary' it will link the patient to the endocrine team for advice. Also 'Insipidus' remains for harmonising publications. Names of conditions have been changed in other specialities. The process of the change to PI which conforms to WHO (World Health Organisation) recommendations will be proposed.
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DOI: 10.1530/endoabs.65.P145

P146

Frequency of pathogenic germline variants in hereditary endocrine tumour genes in patients with discordant cancer phenotypes

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Background
Advances in next-generation sequencing facilitate the simultaneous evaluation of large numbers of cancer predisposition genes (CPGs) in patients with cancer irrespective of family history or tumour phenotype. Several studies have reported the frequent occurrence of germline mutations in CPGs in patients with discordant cancer types raising the possibility of novel gene-cancer associations. The current study aimed to evaluate the significance of germline mutations in monogenic endocrine tumour genes in individuals with such atypical cancers.
Methods
Twelve monogenic endocrine tumour genes were selected including 11 tumour suppressor genes (e.g. *MEN1*, *VHL*, *SDHX*, *NF1*) and *RET* proto-oncogene. The 'typical' tumour spectrum for each gene was defined based on current literature. Pathogenic/likely pathogenic (P/LP) germline variants (as defined using ACMG criteria) were identified in each of the 12 genes in patients with discordant tumour phenotypes from previously reported cancer cohorts (>20 000 patients) and compared to their frequency in a large control population (non-cancer GnomAD cohort ($n=134\,187$ individuals)).
Results
P/LP variants were observed in 10 of the 12 genes evaluated, with *SDHA*, *RET*, and *NF1* most frequently implicated. However, the frequency of germline P/LP variants in individuals with discordant cancers did not differ significantly to that observed in the control population, although it was notable that for the majority of genes the frequency of P/LP variants in the control cohort exceeded estimates of disease prevalence. Loss of heterozygosity data, where available, did not support an aetiological role in the majority of discordant cancers.
Conclusion
Although P/LP germline variants in monogenic endocrine tumour genes may be observed in patients with discordant cancer phenotypes, in most instances these do not appear to be causal. The higher than expected frequency of pathogenic germline variants in the control cohort suggests either reduced disease penetrance, inaccurate estimates of disease prevalence, or possible variant misclassification.

DOI: 10.1530/endoabs.65.P146

P147

Lobectomy for thyroid cancer and thyroglobulin as a tumor marker for long term follow up: current controversies and clarification

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Background
The accuracy of thyroglobulin (Tg) as a tumour marker following lobectomy for differentiated thyroid cancer (DTC) remains controversial. A Tg (<10 µg/l) looked promising in identifying those without clinically apparent recurrence after median 51 months of follow-up. Longer term follow up allows assessment of the diagnostic utility of thyroglobulin in predicting relapse.
Methods
Ninety-nine patients who underwent lobectomy for DTC were retrospectively analyzed using hospital electronic records. Thyroid function and Tg levels were only available for the last ten years.
Results
The mean patient age was 65 ± 12 years (2/3 were women). Median follow-up was 23 years (IQR 12–31 years). Seven died due to non-thyroid related issues. Four patients required further intervention, three had completion thyroidectomy (two for recurrence in contralateral lobe and one for benign nodule) and one had lymph node dissection (further clinical details unknown). Using a Tg cut off <10 ug/dl to predict long-term relapse gave a sensitivity 50%, specificity of 89.5%, positive predictive value 16. 6% and a negative predictive value 97.7% (Table 1).
Conclusion
Serum Tg was elevated in two patients who underwent completion thyroidectomy following lobectomy for DTC but a cut-off of 10 µg/l didn't differentiate recurrent PTC from benign nodularity. One case with recurrent PTC had Tg <10 µg/dl. The high negative predictive value (NPV) of Tg <10 µg/dl for recurrence suggests some benefit in long-term follow-up after lobectomy for DTC, but its low sensitivity limits its clinical utility. Clinical± radiological surveillance remains useful for these patients.

Table 1

	Case 1	Case 2	Case 3
Initial surgery	Left lobectomy	Right lobectomy	Right lobectomy
Initial pathology	PTC$^{\Psi}$	PTC$^{\Psi}$	FTC¶
Tg (µg/dl) at completion thyroidectomy	34	5	21
Thyroid enlargement	Not present	Present	Not present*
Subsequent pathology	Colloid degeneration	PTC	Micro-PTC

Ψ-Papillary thyroid cancer, ¶-Follicular thyroid cancer, *-USG showed nodule of 8 mm.

DOI: 10.1530/endoabs.65.P147

P148

An audit on a teenage and young adult (TYA) neuro-oncology and late effects clinic

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Introduction
Due to improved cancer survival rates, a rising number of CNS cancer survivors face late effects of therapy, such as hormone deficiencies. During adolesecence and young adulthood, specialised transition services are needed to cater for young peoples complex health needs and general needs, such as achieving independence. This study therefore audited a Teenage & Young Adult (TYA) neuro-oncology late effects clinic to identify areas of good practice and areas for improvement.
Methods
The TYA late effects clinic has been running since 2011 and 75 patients are included in the clinic database. The database contains information on known late effects, tumour type and treatment summaries. Patient outcomes were also examined using electronic patient records. A questionnaire was developed to gauge patients' experience of transition and the clinic itself.
Results
64% ($n=48$) patients attending the TYA clinic were at risk of endocrine late effects and underwent regular testing. The commonest tumour types were medulloblastomas and astrocytomas. 22 patients received radiotherapy alone, 22 had radio- and chemotherapy, while 4 only had surgery. Of the 44 patients who received radiotherapy, only 6 had complete therapy details including dose, fraction and duration of treatment. Information on previous chemotherapy was much more complete. The commonest hormone defect was growth hormone deficiency and males were more likely to develop hormone defects than females. Of the 48 patients in this audit, 19 remain under active TYA clinic follow up, 24 have moved on to adult care, 2 were transferred due to tumour recurrence and 3 were lost to follow up. Patient feedback was generally positive, other than that clinic often ran late.
Conclusion
The number lost to follow up is small. There are aspects of the patient experience that could be improved. This audit highlights the need for better oncology treatment summaries to guide endocrine assessment.

DOI: 10.1530/endoabs.65.P148

P149

Prolonged supervised fast for insulinoma – an experience in a District General Hospital Trust

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Introduction
Insulinoma a neuroendocrine *tumour* is diagnosed by inappropriately raised Insulin concentrations during a spontaneous or induced episode of hypoglycaemia. A provocative 72-h supervised fast is done to evaluate suspected inappropriate insulin secretion. Our aim is to see if it is feasible for a shorter duration of fast is enough to confirm Insulinoma.
Method and results
In our Trust we analysed retrospectively in the last 10 years, patients who had prolonged 72 h fast for suspected Insulinoma. 41 patients underwent prolonged (72 h) supervised fast between 2008 and 2017. The time taken to reach significant hypoglycaemia (venous glucose <2.2 mmol/l) was noted. Of the 41 patients, 3 had a positive test confirmed by inappropriately raised Insulin, pro-insulin and c-peptide levels. 2 patients had a positive test within 24 h and 1 within 48 h. The rest of 38 patients were evaluated for reactive hypoglycaemia.
Discussion
All patients who had a positive result developed significant hypoglycaemia mostly within 24 to 48 h of starting the fast. Our numbers were modest due to the rare nature of the disease. We are all aware of the NHS bed pressures and the need for specialist units to do these tests and in the presence of modern parameters like pro-insulin and insulin levels to measure we suggest a 48-h supervised fast to confirm insulinoma. This will be more cost effective and lead to early diagnosis and management.

DOI: 10.1530/endoabs.65.P149

P150

Breast cancer in MEN1: coincidence or association?

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A 38 year old female was identified as carrying a heterozygous pathogenic *MEN1* variant (c.13404delG) through predictive testing, following a diagnosis of familial hyperparathyroidism. Routine screening for hyperparathyroidism and pituitary disease was negative. However, a CT thorax-abdomen-pelvis revealed a 41 mm pancreatic tail mass. Biopsy via endoscopic ultrasound confirmed a well-differentiated (grade 1) pancreatic neuroendocrine tumour (pNET) with MIB1 $<$ 1%. Biochemically, hyperinsulinaemic hypoglycaemia was confirmed following an overnight fast, and subsequently managed by diet prior to definitive surgery. Pre-operative work up with Octreotide scan demonstrated avid tracer uptake in the pancreatic lesion as well as a focal area of uptake in the left breast. Further investigation and subsequent mastectomy confirmed ductal carcinoma in situ pT2 (23 mm) grade 1, N0 (ER positive; HER2 negative). Following this, she underwent a successful pancreatectomy and splenectomy. Patchy insulin staining was seen on the pNET with no lymph node spread. MEN1's association with breast cancer is unclear. Previously, 12 cases of breast cancer were reported in a cohort of 190 MEN1 females (Dreijerink *et al*. 2014). This cohort had early-onset breast cancer diagnosed at a young median age of 48 years, in line with our patient's history. In our patient, loss of heterozygosity (LOH) at the MEN1 locus was seen in the breast tissue and pNET specimen, in keeping with a 'two-hit' hypothesis of oncogenesis, a suggestive but non-definitive clue for causation. However, only 3/9 cases showed loss of heterozygosity (LOH) in the Dutch cohort. Of note, somatic truncating *BRCA2* and *TP53* mutations were also identified in the breast tumour but the variant allele frequency of $<$ 10% for both mutations suggesting that these mutations were sub-clonal rather than the primary genetic driver. This case highlights the need for further studies to determine the potential role of MEN1 in breast cancer development and to guide surveillance strategies.

DOI: 10.1530/endoabs.65.P150

P151

A post implementation audit of a local Chromogranin A service – a step towards individualised patient care

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Background
Neuroendocrine tumours are rare tumours that arise from neuroendocrine cell types which are widespread throughout the body. These tumours can develop in many different organs and secrete a variety of hormones making biochemical monitoring of treatment/progression challenging. Previously patients at Beatson West of Scotland Cancer Centre were monitored using either a full gut hormone profile (GHP) or chromogranin A and B (CGs) measured at Charing Cross Hospital. A new chromogranin A (CgA) service was introduced in Scotland in September 2018 using the CisBio ELISA assay. Patients undergoing monitoring initially had paired analysis due to the expected variation between assays. This audit aims to identify the most appropriate marker for ongoing follow-up on an individual patient basis.
Method
Seven months of data was extracted from the laboratory system to include all requests for local CgA, GHP, and CGs. Patients were included if they had two paired samples within this time period. Clinical details were collated from the clinical portal system to include where available type of tumour, treatment and imaging results.
Results
Forty one patients were identified; nine patients with pancreatic tumours were excluded as the local protocol in this group is full GHP. Of the 32 remaining patients, 69% could be monitored using the local CgA assay. A group of patients still require monitoring by the Charing Cross assay, 12.5% are CgB secretors only and 9% have normal local CgA but abnormal CGs. The remaining 9% have discordant results between assays and more paired data is required before a decision is made.
Conclusion
The new local CgA assay is a useful marker for follow up in 69% of patients. Individualisation of monitoring can improve patient care and cost effectiveness.

DOI: 10.1530/endoabs.65.P151

P152

The expression pattern of miR-16, 21, 145, and 375 in plasma of breast cancer patients at different clinical stages

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Current challenges in the management of breast cancer includes a continuous search for sensitive and specific minimally invasive biomarkers that can be exploited to detect early neoplastic changes, thus facilitating the detection of breast cancer at an early stage, as well as for monitoring the progress of patients with breast cancer and their response to treatments. This study investigated the expression pattern of miR-16, 21, 145, and 375 in plasma of breast cancer patients at different clinical stages of the disease. Informed consents were obtained from forty-nine (49) participants diagnosed with breast cancer and receiving chemotherapy treatment at the Lagos University Teaching Hospital (LUTH) and twenty-seven (27) healthy individuals. miRNA was isolated from plasma, reversed transcribed and quantified using SYBR green chemistry semi-quantitative PCR. Cases comprised of 2(5.6%) stage-I, 13(36.1%) stage-II, 12(33.3%) stage-III patients, and 9(25.0%) Stage IV patients. The was a non-significant increase in miRNA-16 and 21 expression levels in BC compared with the control group; miRNA-145 was non-significantly downregulated as the disease progressed from stage II to IV; while there was no observable difference between BC cases and the control group. The data suggests the possible use of miRNA 16, 21, 145, and 375 expression levels as diagnostic and prognostic markers in breast cancer management.

DOI: 10.1530/endoabs.65.P152

P153

Ipilimumab-induced hypophysitis with normal pituitary function: a series of 3 cases

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Introduction
Hypophysitis has been recognised as a frequent endocrine related side effect of immunotherapy with the CLTA-4 inhibitor Ipilimumab, with a prevalence of up to 17.4%. The most common symptoms of hypophysitis are headache and signs/symptoms of hypopituitarism. Whilst some patients have an enlarged pituitary on MRI, this is frequently normal. ACTH and TSH deficiencies are most common, but all anterior and posterior pituitary hormonal axis may be affected. Hypopituitarism may be transient, but cortisol deficiency usually persists.
History and investigations
Three patients treated with Ipilimumab (two in combination with Nivolumab) for metastatic melanoma developed evidence of hypophysitis with diffuse pituitary enlargement on MRI scans 1 to 3 months post initial dose of immunotherapy. One of the patients was treated with methylprednisolone as treatment for severe hypophysitis. However biochemical investigation in all three did not show full hypopituitarism. One patient had transient low cortisol, but has had a normal Short Synacthen test off treatment 5 years later. One had normal pituitary function prior to receiving steroids for hepatitis, and a peak cortisol on an ITT of 451 nmol/l after completion of steroids. The third also required long term prednisolone for hepatitis, but has had a 0900 h cortisol of 230 nmol/l with normal ACTH, pending further testing. None had secondary hypothyroidism or other pituitary hormone deficiencies. Repeat MRI scans showed normalisation of pituitary appearances in all three patients.
Conclusion
Hypopituitarism due to hypophysitis is a common adverse event of Ipilimumab. Although it has been recognised that only half of patients with hypopituitarism have an abnormal MRI, we report three cases with pituitary enlargement on MRI in keeping with hypophysitis but without subsequent clinically significant endocrine dysfunction. Morphological changes to the pituitary gland are dynamic and may not correlate to hypopituitarism.

DOI: 10.1530/endoabs.65.P153

P154

Checkpoint inhibitors and immune related diabetes mellitus: a case series

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Introduction
Checkpoint inhibitors (CPi) are finding a place in the treatment algorithm of an increasing number of cancers. Immune-related (ir) endocrinopathies are frequent side-effects. Diabetes mellitus (irDM) is infrequent, but often presents acutely and can be potentially life-threatening There are ~60–70 cases characterising irDM in the literature. We describe 4 cases of irDM to add to the understanding of this condition. All four patients were undergoing treatment for stage 3C or metastatic melanoma. None had a personal or family history of diabetes. Three of the patients received combination therapy with a CTLA4 and PD1 inhibitor (ipilimumab 3 mg/kg and nivolumab 1 mg/kg), and the additional patient received single agent anti-PD1 therapy (pembrolizumab). The age of the patients ranged from 57 to 72 years, and three were male. Clinical presentation of irDM occurred at a variable time point following initiation of CPi therapy (13, 21, 36, and 37 weeks). All presented with classical symptoms of diabetes (osmotic symptoms/weight loss +/− vomiting). Three of the four cases fulfilled the criteria for diabetes ketoacidosis at presentation. The fourth case showed evidence of ketosis, but just failed to meet the criteria for acidosis. Plasma glucose levels ranged 28.7–30.3 mmol/l, and HbA1c values were 66, 68, 71, and 100 mmol/mol. All were managed according to the local DKA protocol, and on resolution were changed to a maintenance basal-bolus insulin regimen. Anti-GAD antibodies were negative in three of the four cases. One patient had previously developed both ir-hepatitis and ir-hypophysitis, and a further patient a ir-destructive thyroiditis.
Conclusion
IrDM presents acutely with clinical and biochemical features of insulin deficiency that require insulin treatment. Combined anti-CTLA4 and PD1 therapy represents the greatest risk, with PD1 monotherapy representing a lower but significant risk. Patients should be educated in respect to this side-effect, and to present acutely to medical care should symptoms occur.

DOI: 10.1530/endoabs.65.P154

P155

Carney's triad due to SDHA gene mutation

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Carney's triad; a diagnosis based on the presence of three associated neoplasms; epithelioid *leiomyosarcoma*, pulmonary *chondroma*, and extra-*adrenal paraganglioma* remains a rare diagnosis. Here we report a 52-year-old female investigated for chronic cough. Initial chest X-ray demonstrated calcified masses, and CT thorax confirmed a left pulmonary lesion measuring 41 mm in diameter with 3 adjacent smaller nodules up to 20 mm. A chondroid pattern of calcification, consistent with pulmonay chrondoma, was noted. Completion imaging identified multiple abnormalities including multiple indeterminate liver lesions, up to 8 mm in diameter, an 11 mm nodule arose from the mid oeosophagus, a 24 mm soft tissue mass involving the bladder (the most common site for epithelioid leimyosarcoma), a 22 mm left ovarian cyst, and a 10 mm left adrenal nodule. Biochemical investigations including renal profile, liver profile, bone profile, plasma metanephrines, and spot urinary 5-HIAA were unremarkable. Cystoscopy failed to identify a bladder mass, and thus biopsy of the suspected lesion has not been feasible to date. Gastroscopy, and subsequent endoscopic ultrasound, demonstrated several oesophageal submucosal lesions, histologically consistent with leiomyoma. MRI liver demonstrated several small haemangiomata and areas of focal nodular hyperplasia. Interval CT chest and MRI pelvis demonstrated stability in the pulmonary chondroma and bladder lesion. In the context of multiple primary tumours, genetic analysis was undertaken revealing a germline mutation of SDHA. SDHA mutations are becoming increasingly recognised as a cause of familial phaeochromocytoma/paraganglioma syndromes, in addition to other related tumours. SDHA mutation has been reported to result in Carney's triad. In the context of pulmonary chondroma, suspected bladder leimyosarcoma, and germline SDHA mutation, we thus conclude that this patient is at high risk for completing Carney's triad and thus requires further diagnostics and close longitudinal follow-up.

DOI: 10.1530/endoabs.65.P155

P156

Insulinoma causing remission of diabetes mellitus type 2

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We present the case of a 77-year-old woman with a medical history of diabetes mellitus type 2 and hypothyroidism who was admitted to hospital after having had episodes of recurrent symptomatic hypoglycaemia. The patient had diabetes mellitus type 2 for 26 years and this had gone into remission over the previous 2 years: she had been having recurrent hypoglycaemia necessitating reduction in insulin doses and then subsequent discontinuation of therapy altogether. There was a history of weight loss, without other red flag features, and the clinical situation was proposed to be secondary to the patient's low carbohydrate diet and iatrogenic hyperthyroidism. Several months after insulin therapy had been discontinued the patient was admitted with severe hypoglycaemia. As an inpatient, she was noticeably dependent initially on intravenous dextrose infusions then frequent sugary drinks, with her blood glucose levels plummeting overnight when unable to maintain dietary intake. Supervised fast yielded blood glucose levels of 2.0 mmol/l with an C-peptide level of 2.61 nmol/l ($<$1.12 nmol/l) and an insulin level of 24.9 mU/l ($<$13 mU/l). The patient had neuroglycopaenic symptoms at that time which resolved when the blood glucose was corrected. HbA1c was 19 mmol/mol and the urinary sulphonyurea screen was normal. CT imaging revealed a 1.6 cm homogenously enhancing nodule in the tail of the pancreas. Due to the high risk of hypoglycaemia and intolerance of diazoxide therapy the patient underwent enucleation of her pancreatic mass. Pathology confirmed a well differentiated grade 2 Insulinoma. Euglycaemia was achieved for a short period following surgery but reverted to hyperglycaemia as her weight increased. Insulinoma is a rare cause of hypoglycaemia and rarer still in conjunction with diabetes mellitus type 2. We discuss when to reasonably suspect insulinoma in the patient with diabetes, drawing experience from previous case reports.

DOI: 10.1530/endoabs.65.P156

P157

Audit of biochemical screening for multiple endocrine neoplasia type 1 in patients diagnosed with pancreatic neuroendocrine tumours

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Background

Pancreatic Neuroendocrine Tumours (pNETs) can be associated with cancer susceptibility syndromes such as Multiple Endocrine Neoplasia type 1 (MEN1). MEN1 increases a person's chance of developing pNETs, which are the main cause of mortality in this cohort. A diagnosis of pNETs, therefore, provides the opportunity for detection of associated MEN1 and subsequent identification of asymptomatic relatives who would then undergo relevant clinical, biochemical and radiological surveillance.

Aims

The primary aim of this audit was to determine whether the local Wessex guidelines recommending biochemical screening for pNET patients were being followed. Screening for MEN1 consists of measuring serum calcium, parathyroid hormone (PTH), prolactin, IGF-1 (where there is clinical suspicion of acromegaly) as well as fasting gut peptide levels (10% of pNETs are estimated to be functional tumours).

Methods

A cohort of 64 patients [25 (39%) males and 39 (61%) females, average age of patients was 64.9 ± 16.4 years] with a diagnosis of pNETs (ranging from grade 1 to grade 3) was retrospectively reviewed. In each patient, clinical & laboratory records were analysed in regards to whether they had been screened in accordance with our local guidelines.

Results

100% of patients had calcium tested. 33% had PTH tested. 72% had results for a gut peptide assay. Prolactin was only tested in 25% of the cohort with 22% having a result for IGF-1. Within the cohort 6 patients were known to have MEN1.

Conclusion

The results of this audit indicated variability in the adherence to recommended screening. Whilst 100% of patients had calcium checked, investigations for PTH (especially in those with high calcium), prolactin and the gut peptides were not performed at the required level. These findings were shared with the multi-disciplinary NET MDT professionals to emphasise the guidelines with the aim to repeat the audit after a period of implementation.

DOI: 10.1530/endoabs.65.P157

P158

Palliative electrochemotherapy treatment in a patient with advanced thyroid papillary carcinoma with cutaneous metastases

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Advanced papillary thyroid carcinoma (PTC) with cutaneous metastases may cause pain, ulceration and bleeding. Electrochemotherapy (ECT) is a minimally invasive oncologic treatment of tumours located in the skin and subcutaneous tissue. The electric pulses potentiates the toxicity of a cytostatic agent entering the tumour cell. It is highly effective especially to relieve pain and improve quality of life. The adverse events are local and transient. A case of progressive metastatic PTC who developed bleeding cutaneous metastases treated with ECT is described. A 85-year-old male with a 18-months history of a cervical nodule with indolent growth and multiple cutaneous lesions in the scalp submitted to surgical excision. The cervical ultrasound (US) revealed multiple and suspicious thyroid nodules and a nodule located in the supraclavicular right region. Fine-needle aspirate (FNA) from those nodules suggested papillary thyroid carcinoma and the computed tomography (CT) revealed an extensive metastization into cervical lymph nodes, bone, lung and liver. In the follow-up, the patient developed a new multiple scalp nodules with 20 mm, firm and non-painful. The CT excluded bone invasion of the skull. FNA of the lesions was compatible with papillary thyroid carcinoma metastasis and thyroglobulin was >30 000 ng/ml in needle washout fluid. The lesions developed active bleeding and did not respond to local treatment with silver nitrate. The patient was submitted to an ECT session with IV bleomycin (15 000 UI/m^2) administered in a bolus prior to the administration of electroporation pulses targeting the described lesion. The procedure took place in the ambulatory surgery unit under general anesthesia. The bleeding stopped in the following days and clinical complete response was observed five months after ECT. The patient did not develop complications related to bleomycin toxicity. ECT seems to be a safe and effective option for local palliative treatment in advanced PTC patients with improvement of local symptoms.

DOI: 10.1530/endoabs.65.P158

P159

Recurrent hyperparathyroidism in a patient with multiple endocrine neoplasia type 1 (MEN1) after total parathyroidectomy with autotransplantation unmasked by depression and vague abdominal pain

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Total parathyroidectomy with autotransplantation of parathyroid tissue is one of the treatment modalities for primary hyperparathyroidism in Multiple endocrine neoplasia type 1 (MEN1). Many of these patients are young and recurrence may take decades to emerge. We present a case of a 45-year-old woman who was diagnosed with MEN syndrome type 1 at the age of 12. Over the years, she underwent multiple surgical interventions including pituitary macroprolactinoma resection resulting in panhypopituitarism, pancreatectomy for insulinoma resulting in insulin dependent diabetes and parathyroidectomy. In order to avoid future hypoparathyroidism, she had 3 parathyroid glands removed with autotransplantation of 4th parathyroid gland in the flexor surface of the left arm. Ten years following autotransplantation, she developed depression with recurrent vague abdominal pain and constipation which necessitated referral to departments of psychiatry and gastroenterology. She underwent extensive investigations and treated with antidepressants. Mild hypercalcemia was observed which triggered a referral to endocrine clinic. Further assessment revealed persistently elevated parathyroid hormone level of 15.6 pmol/l. Corrected serum calcium was elevated (2.68 mmol/l) with low phosphorous level of 0.77 mmol/l. 25-hydroxy-vitamin D and 1,25-dihydroxyvitamin D were both in the normal range. Clinical and laboratory data confirmed the diagnosis of recurrent hyperparathyroidism. Once the diagnosis was established, she had an uneventful surgical removal of the autotransplanted parathyroid gland and she maintained normocalcaemic state. Careful history exploration and surgical resection are two important components of successful management of this patient.

DOI: 10.1530/endoabs.65.P159

P160

Irradiation and endocrinopathies: multiple complications in a single patient

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Endocrinopathies are common complications following cancer therapy and may occur decades later. We present a case of 37 year old lady with a background of chronic myeloid leukaemia (CML) which was treated with sibling allogenic stem cell transplant and total body irradiation in 2002. She was noted to have elevated calcium levels with raised PTH 10 years later. In view of young age, she underwent genetic screening for MEN1 through buccal swab as her lymphocytes were not suitable due to stem cell transplant from sibling, which was negative. She was then diagnosed with primary hyperparathyroidism as a complication of total body irradiation. During the investigations, she was noted to have a sub-centimetre benign looking thyroid nodule which on repeat ultrasound increased in size to 2.8 cm and showed increased central vascularity (U3). She subsequently had a fine needle aspiration twice which showed hyperplastic nodule consistent with benign cytology (Thy2) both times. However, in view of previous CML treated with irradiation, she underwent elective hemithyroidectomy in addition to parathyroidectomy. Her histology showed left inferior hypercellular parathyroid and encapsulated angioinvasive follicular carcinoma. She became normocalaemic post-surgery but in view of follicular carcinoma, she underwent completion

thyroidectomy with subsequent radioiodine treatment. This case highlights many important learning points. First, whole body irradiation is associated with hyperparathyroidism which is lesser known long term complicationand therefore, it is important to monitor calcium levels annually in these patients. In addition, irradiation also increases the risk of secondary malignancies including thyroid neoplasms. There should be high index of suspicion for further investigations of thyroid nodules in such cases. In addition, it is important to remember that blood samples could not be used for DNA testing in patients with stem cell transplant and buccal swabs, although not gold standard could be used as an alternative.

DOI: 10.1530/endoabs.65.P160

P161

A rare case of Small cell lung carcinoma with dual ADH and ACTH secretion

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This is a case of a patient diagnosed with small cell lung carcinoma after presenting with severe hyponatremia due to syndrome of inappropriate antidiuretic hormone secretion (SIADH) who was readmitted 7 months later with refractory hypokalemia and hyperglycaemia due to ectopic adrenocorticotrophic hormone secretion (EAS). A 65 year-old man presented in November 2018 with symptoms of nausea, vomiting, headaches and blurred vision. On examination he was clinically euvolemic. Laboratory results revealed sodium of 117 mmol/l without other electrolyte abnormalities, serum osmolality 256 mOsm/kg, cortisol 322 nmol/l, urine sodium 112 mOsm/kg, urine osmolality 499 mOsm/kg and normal TFTs, results consistent with SIADH. He had no drug history and was an ex-smoker. Hyponatremia was managed with hypertonic saline and demeclocycline. CT Scan and PET-CT showed left hilar mass but no metastasis (stage T2aN0M0). Bronchosopic guided tissue biopsy + histology confirmed SCLC immunoreactive with CD 56, synaptophysin and chromogranin. In the following weeks he completed a full course of chemotherapy and radiotherapy. The patient was re-admitted in May 2019 with severe hyperglycaemia and refractory hypokalemia associated with hyperpigmentation, peripheral oedema and increased abdominal adiposity. Biochemistry showed baseline 0900 h cortisol of >1650 nmol/l without suppression following dexamethasone, urine cortisol >6905 nmol/24H and high ACTH levels, results compatible with ectopic ACTH secretion from the SCLC. Unfortunately our patient's condition deteriorated rapidly soon after being diagnosed with Cushing's syndrome due to EAS on top of SIADH and soon developed pancytopenia with acute liver failure and sadly passed away 14 days after diagnosis of ectopic ACTH secretion from SCLC. So far only 8 cases with SCLC with dual SIADH and EAS have been described in literature, the development of EAS being associated with the worst prognosis and shortest median survival.

DOI: 10.1530/endoabs.65.P161

P162

Transient adrenal insufficiency in a patient with an insulinoma

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A 45-year-old man with obesity (BMI 36 kg/m^2) was admitted with a 12-hour history of headache and confusion and managed for viral meningitis. Treatment was discontinued after CSF viral PCR was negative. At presentation, he was hypoglycaemic with a capillary glucose of 1.6 mmol/l. Past medical history was not significant and there were no similar episodes previously. He denied taking insulin, other medications, illicit drugs or alcohol. Initial investigations revealed normal full blood count, liver and kidney function tests, C-reactive protein and normal CT head. Our patient continued to experience recurrent hypoglycaemic episodes. Biochemical investigations revealed normal pituitary hormone profile, thyroid function tests and coeliac screen. Short synacthen test (SST) revealed a baseline cortisol of 193 nmol/l and 30-min cortisol 407 nmol/l. Subsequently, SST was also abnormal. ACTH level was 4.3 pmol/l (2–11). Antiadrenal antibodies were negative. A diagnosis of idiopathic adrenal insufficiency was made and the patient initiated on oral hydrocortisone, but continued to have hypoglycaemic episodes. Serum insulin and insuin C-peptide levels were inappropriately elevated in keeping with endogenous hyperinsulinaemia (serum insulin 276 pmol/l, insulin C-peptide – 1756 pmol/l) during a hypoglycaemic episode on the 72-h fasting test. Somatomedin C was normal {17.2 nmol/l (7.7–26)}. CT abdomen with contrast revealed a 2.3×2.1 cm lobulated mass in the pancreatic tail. The patient was initiated on diazoxide and referred to a pancreatic surgeon. He underwent partial-pancreatectomy and histology revealed an insulinoma. Adrenal insufficiency persisted for 12 months (base line and 30-min cortisol, 159 and 418 nmol/l respectively) and only resolved after 15 months (baseline cortisol and 30 min cortisol 259 and 520 nmol/l), when hydrocortisone was stopped. The combination of insulinoma and transient adrenal insufficiency is rare; our case report suggests a potential association, highlighting the need for further research.

DOI: 10.1530/endoabs.65.P162

P163

Impact of diabetes education in patients with newly diagnosed diabetes

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Diabetes education plays a vital role especially in newly diagnosed patients to prevent long-term complications and hospital admissions. We present a 68-year old female who was admitted with nausea, vomiting and poor oral intake. She was discharged two weeks ago after having complete pancreatectomy, splenectomy and left adrenalectomy for pancreatic cancer and a left adrenal mass. She did not have past medical history of diabetes and was commenced on basal bolus insulin after surgery but admitted to omitting the insulin. Examination showed signs of dehydration, a healed surgical scar but no localising signs of infections. Investigations revealed hyperglycaemic ketosis without acidosis. She was initially given variable rate insulin infusion (VRII) with transition to subcutaneous insulin when she was able to eat and drink. VRII was restarted 24 h later by the admitting team due to persistent hyperglycaemia and ketonaemia. She was referred to diabetes team and was noted to have several hypoglycaemic episodes on VRII. She had a glucometer and ketometer, but was not confident enough to manage diabetes related sick days independently. She was provided with extensive education by diabetes specialist nurses and dietitians. Basal bolus insulin was recommenced based on re-calculation of insulin requirements and no further hypoglycaemic or hyperglycaemic events were noted afterwards. Patients develop diabetes immediately after total pancreatectomy and, unlike patients with other types of diabetes, have no honeymoon phase. They are at high risk of acute and chronic diabetes complications and need more vigorous and ongoing diabetes education. If admitted to the hospital, early referral to diabetes team can prevent further complications and reduce the length of hospital stay.

DOI: 10.1530/endoabs.65.P163

P164

Case report on Immunotherapy mediated hypocortisolemia

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63 year old gentleman, admitted in Nov 2018. Feeling generally unwell, decreased appetite, lethargy and poor mobility. Known lung cancer (diagnosed January 2018) On Immunotherapy last received in October 2018CT scan (September 2018) after 4 cycles of Pembrolizumab–excellent response to treatment. Routine blood tests were normal apart from a raised CRP at 551 and white cell count. A random cortisol level was done and found to be low at 135. Blood, urine, sputum and stool cultures were all negative. He was commenced on

intravenous antibiotics for sepsis but had no clinical improvement after 48 h. Discussed with oncology team who advised a CT scan of head, thorax, abdomen, pelvis. This was done and revealed no evidence of disease progression. Advice was then given to commence patient on Prednisolone 1 mg/kg. There was a clinical and physical improvement in the patient with a couple of days. Patient was discharged home with oncology and endocrine follow up with advice on tapering steroid dose.

Discussion

Potential for immunomodulation to result in an increased incidence of autoimmune disease against endocrine organs. Agents are directed against immune check point molecules such as CTLA-4 or PD-1 and these modulate T cell response to malignancy- enhancing activity and proliferation leading to immune related adverse events. Pembrolizumab is anti-PD-1. Caused by a type II hypersensitivity reaction resulting in hypophysitis. Screen for other causes of pituitary dysfunction and hormone profile assessment. ACTH/cortisol measurements – low. Secondary hypothyroidism – low TSH & FT4. Secondary hypogonadism. Growth hormone axis is spared. With emerging immunotherapy use, awareness of drug related adverse effects is important. Pituitary hormone profile should be appropriately monitored throughout immunotherapy and treatment instituted soon. Physicians should be aware and patients should be educated to notify symptoms promptly. A joint pathway of surveillance with oncologists is currently in process.

DOI: 10.1530/endoabs.65.P164

P165

A case of pituitary metastatic deposit from breast cancer

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Introduction

Metastatic lesion in the pituitary is a rare condition with most of them being asymptomatic. Breast cancer is the most frequent primary location and the overall prognosis is poor. We describe the case of a lady with this condition, who presented to our unit with bitemporal hemianopia.

Case

A 65 year old lady with history of breast cancer (surgical excision with chemoradiotherapy 4 years ago, HER2 negative, currently in remission) presented with bitemporal hemianopia. Endocrine testing showed hypocortisolism and secondary hypothyroidism and commenced on replacement therapy. MR Pituitary showed a pituitary lesion which was radiologically consistent with adenoma, but also revealed a posterior fossa lesion. There was significant pressure on optic chiasm which accounted for her visual field loss. Whole body imaging showed lesions in brain and lungs consistent with metastatic deposits. She underwent sellar decompression to protect her vision and is undergoing chemotherapy.

Discussion

Metastatic pituitary deposits are estimated to be around 1.8% of surgically resected pituitary lesions and they remain a rare entity. Upto 3.6% of all intracranial mets are estimated to be in the pituitary. About a quarter manifest as Diabetes insipidus and panhypopituitarism is found in a quarter as well. Most cases involve the posterior pituitary and the blood supply to this area derived from systemic circulation has been proposed to play a role. Similar to our case, incidence was 9.3 times more frequent with breast cancer, followed by lung, thyroid and renal cell cancer. Approaches to treatment have included surgery, chemotherapy, radiotherapy, radiosurgery and hormonotherapy and all modalities carry risk of panhypopitutarism. Prognosis remains poor with an estimated survival of 13.6 months from diagnosis of the Pituitary metastasis. A high degree of suspicion in cancer patients showing extreme lethargy or other symptoms of hypopituitarism might help earlier diagnosis and treatment.

DOI: 10.1530/endoabs.65.P165

Metabolism and Obesity

P166

Obesity-induced changes in hepatocyte and skeletal myocyte expression of mRNAs encoding islet GPCR peptide ligands

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Introduction

Insulin-sensitive tissues such as liver and skeletal muscle modify their gene expression under conditions of obesity-induced insulin resistance, and some of these gene products may be released to maintain glucose homeostasis. This study aimed to identify mRNAs encoding liver and skeletal muscle peptides that have the potential to regulate β-cell function by binding to islet GPCRs, and to quantify changes in expression of these liver and muscle mRNAs in obese mice.

Methods

Livers and gastrocnemius muscles were extracted from C57BL/6 mice fed either a chow diet (CD:3% fat/4% sugar) or high-fat-high-sugar diet (HFHSD:20% fat/10% sugar) for 34 weeks and qPCR was used to quantify mRNAs encoding previously validated islet GPCR peptide ligands.

Results

GTTS and ITTs demonstrated overt insulin resistance on a HFHSD (**GTT**:CD 0 min(9.12 ± 0.97 mmol/l glucose), 30 min(14.25 ± 1.71), 120 min(9.35 ± 1.24); HFHSD 0 min(9.46 ± 0.81), 30 min(29.42 ± 1.34), 120 min(12.54 ± 1.74), $P < 0.001$, $n = 4$; **ITT**: CD 0 min(8.92 ± 1.25 mmol/l glucose), 30 min(6.07 ± 1.14), 60 min(6.57 ± 1.07); HFHSD 0 min(9.18 ± 0.22), 30 min(9.94 ± 1.25), 60 min(10.34 ± 0.52), $P < 0.05$, $n = 4$). Our qPCR screening demonstrated that 107 and 76 islet GPCR ligand mRNAs were expressed above trace levels in hepatocytes and myocytes respectively. Several of these mRNAs showed altered expression in CD and HFHSD hepatocytes and myocytes. In particular, *Col3a1* and *Cort* mRNAs were up-regulated (**control**:1; **upregulation**(>1): 3.81 ± 0.61- and 11.49 ± 3.65-fold) in insulin resistant hepatocytes and myocytes, respectively, while other peptide mRNAs, including *Pyy* and *Wnt5b*, were down-regulated (**downregulation**: (<1): 0.006 ± 0.001- and 0.46 ± 0.12-fold) in HFHSD liver and muscle, respectively.

Discussion

This focused approach of GPCR ligand expressome screening has the potential to define novel cross-talk from hepatocytes and myocytes to islet β-cell GPCRs, with the future aim that such liver- and skeletal muscle-derived peptide ligands (or stable derivatives) may be developed as new therapies for diabetes.

DOI: 10.1530/endoabs.65.P166

P167

Sarcopenic phenotypes are associated with an increased risk of type 2 diabetes: findings from the Korean Genome and Epidemiology Study (KoGES)

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The present study aimed to explore the relationship of sarcopenia, with or without the presence of obesity, with the risk of developing type 2 diabetes. We conducted a cross-sectional analysis of 2981 subjects in the Korean Genome and Epidemiology Study. The diabetes status of each subject was determined by using a 75 g oral glucose tolerance test, and body composition was estimated via dual-energy X-ray absorptiometry. The skeletal muscle mass index (SMI, %) was obtained by calculating the total skeletal muscle mass as a percentage of body weight. In the non-diabetic subjects, the SMI exhibited an independent negative correlation with the homeostasis model assessment of insulin resistance value (P for trend < 0.001). Among subjects of age 60 years or older with pre-diabetes or newly diagnosed diabetes, a substantial increase in the prevalence of sarcopenia (without obesity) and sarcopenic obesity (SO) was observed, as compared to patients with normal glucose tolerance status. Furthermore, the odds ratios (OR) for pre-diabetes and newly diagnosed diabetes were significantly greater for subjects of 60 years or older in the SO group compared to the normal phenotype (neither obesity nor sarcopenia) group, after multiple adjustments (OR = 2.45, 95% CI = 1.81–3.32), and similarly, the sarcopenia group was at a relatively higher risk for pre-diabetes and newly diagnosed diabetes (OR = 1.62, 95% CI = 1.15–2.28). These statistical significances were not observed for the middle-aged group of subjects. In conclusion, sarcopenia and SO display strong association with an increased risk of pre-diabetes and newly diagnosed, or early phase diabetes in older Korean adults. These findings suggest that the age-related loss of muscle mass may be an independent risk factor for the progression of pre-diabetes to early phase type 2 diabetes.

DOI: 10.1530/endoabs.65.P167

P168

Long term impact of sleeve gastrectomy on metabolic parameters in morbidly obese patients

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Background
A large body of evidences have demonstrated that metabolic surgery is associated with significant and durable weight loss as well as a significant improvement of obesity-related comorbidities. The aim of our study was to evaluate the long term impact of gastric sleeve on metabolic parameters in morbidly obese patients.
Materials and methods
We evaluated 95 (67 women) severely obese patients (mean age 43.4 ± 10.69 years) before and approximately 5 years after sleeve gastrectomy performed in a highly specialised centre. Anthropometric parameters, lipid profile, glucose and insulin levels were measured. We also determined the change in metabolic syndrome prevalence and looked for predictors of MetS long term remission.
Results
5 years after gastric sleeve, mean BMI decreased from 44.6 ± 8.1 kg/m^2 to 34.2 ± 6.25 kg/m^2, $P < 0.00$. Excess BMI loss (EBL) ranged from 0 to 135%, with a mean value of 55.3%. 51.5% of our patients maintained an EBL > 50% at the 5 years follow-up. The best results on weight loss were observed in young patients, not affected by MetS, with lower initial BMI. Mean levels of HOMA-IR decreased from 5.5 ± 4.9 to 2.5 ± 2.4, $P < 0.001$. HOMA-IR % variation positively correlated with BMI % variation ($r = 0.317$, $P = 0.006$) and waist circumference % variation ($r = 0.461$, $P < 0.001$) but we found no relationship between HOMA-IR % variation and baseline BMI. We observed a significant improvement in triglycerides and HDL-cholesterol levels, but not in total or LDL-cholesterol. Metabolic syndrome prevalence decreased from 64.9% to 22.7%. In multivariate analysis, % EBL and baseline HOMA-IR were the significant predictors of MetS remission.
Conclusions
5 years after sleeve gastrectomy we recorded maintenance of a significant weight loss and improvement in insulin resistance, lipids metabolism, and metabolic syndrome prevalence, independent of the baseline BMI.

DOI: 10.1530/endoabs.65.P168

P169

Intravascular subcutaneous adipose tissue blood flow measured with Doppler ultrasound for experimental medicine studies

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Background
Adipose tissue blood flow (ATBF) is important for delivering nutrients and oxygen to adipose tissue (AT), and distributing adipokines and metabolites into the circulation. ATBF has been measured with the ^{133}Xenon wash-out technique (gold standard), microdialysis, laser Doppler Fluximetry, and contrast-enhanced ultrasound. However, due to decline in world-wide ^{133}Xenon production and the invasive nature of other techniques, an alternative method for ATBF measurements in clinical studies is needed.
Objective
To explore intravascular AT Doppler ultrasound as a proxy method for measuring ATBF, by establishing technical feasibility, reproducibility, and sensitivity of the method to detect ATBF changes in response to an oral glucose drink.
Methods
Twelve individuals (9 females, 3 males, BMI range: 19.8–24.4 kg/m^2, age range: 24–58 years) were recruited. Using a Philips CX50 system, suitable abdominal subcutaneous AT veins were identified, and ATBF was measured with Doppler ultrasound at 10-min intervals. Measurements were taken by a single operator and repeated up to three times at each time-point. Following 30 min of basal ATBF measurement, a 75 g oral glucose drink was ingested to determine the postprandial ATBF response for 120 min.
Results
Basal ATBF was 2.1 ± 0.8 ml/min, peaking at 5.1 ± 1.3 ml/min at 90 min post-glucose ($P = 0.016$ compared to baseline, Wilcoxon signed-rank test). ATBF then dropped to 2.7 ± 1 ml/min at 120 min ($P = 0.010$ compared to peak). The coefficient of variation of repeated measurements ranged from 31.5% ± 5.8 for baseline and from 26.2% ± 6.3 for peak ATBF measurements.
Conclusions
ATBF measurement with intravascular AT Doppler ultrasound seems feasible. The method is sensitive to record the expected ATBF increase following glucose ingestion. However, as expected, there is large inter- and intra-individual variability, which is commonly observed with ultrasound measurements. More studies are needed to explore the feasibility of the method in determining ATBF in other populations, establish inter-operator variation and to establish a model of ATBF responses.

DOI: 10.1530/endoabs.65.P169

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Chronic disruption of endothelial Insulin/IGF1 signaling pathway enhances whole body insulin sensitivity

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Type 2 diabetes is preceded by insulin resistance, followed by increased endothelial cell production of superoxide and reduction in bioavailability of the vasoprotective signalling molecule, nitric oxide (NO). We demonstrated in preclinical models that type 2 diabetes also causes resistance to insulin-like growth factor-1 (IGF-1) mediated glucose lowering and endothelial NO release. This study aimed to examine the effect of the endothelial cell-specific combination of insulin and IGF-1 resistance on glucose homeostasis and NO availability. We generated mice expressing mutant IGF-1 receptors (mIGF-1R) which form non-functional hybrid receptors with endogenous insulin receptors (IR) and IGF-1R under the control of Tie2 promoter-enhancer, to induce insulin and IGF-1 resistance specifically in endothelial cells. Despite endothelial insulin and IGF-1 resistance, mutant IGF-1R endothelial cell over-expressing mice (mIGFREO) had enhanced insulin and IGF-1 mediated glucose lowering, lower fasting free fatty acids and triglycerides. In hyperinsulinaemic–euglycaemic clamp studies, mIGFREO had increased glucose disposal and increased glucose uptake into muscle and adipose tissues in response to insulin. mIGFREO had reduced endothelial cell NADPH oxidase 2 (Nox2) expression and increased endothelial cell NADPH oxidase 4 (Nox4) expression. Consistent with increased Nox4, mIGFREO endothelial cells generated increased hydrogen peroxide (H_2O2) with no increase in superoxide. Furthermore, *in vivo* treatment with catalase, a H_2O2 dismutase restored insulin tolerance to wild type levels in mIGFREO. mIGFREO mice demonstrated a decrease in the expression of the small non-coding RNA, miR-25 in endothelial cells, which is also negative regulator of Nox4. Combined insulin and IGF-1 resistance at the endothelial level leads to a potentially favourable adaptation including a switch in the balance in oxidant species generation from Nox2-derived superoxide, seen in pure insulin resistance to a miR-25 regulated Nox4-derived H_2O2 generation which enhances whole body insulin sensitivity.

DOI: 10.1530/endoabs.65.P170

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5β-reductase (AKR1D1) isoforms differentially regulate natural and synthetic glucocorticoid clearance and glucocorticoid receptor activation *in vitro*

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Metabolic syndrome and its hepatic manifestation, non-alcoholic fatty liver disease (NAFLD), are increasing in prevalence. Steroid hormones are established regulators of metabolic phenotype. 5β-reductase (AKR1D1) is highly expressed in human liver, inactivating steroid hormones, including glucocorticoids and androgens. The human AKR1D1 gene contains 9 exons; six splice variants have been identified and three lead to functional protein isoforms (*AKR1D1-001*, *-002*, and *-006*). The AKR1D1-002 isoform is the most well-characterised and we have shown that it is able to modulate hepatic glucocorticoid availability and glucocorticoid receptor (GR) activation. However, the potential of the other AKR1D1 isoforms to regulate steroid hormone availability is unknown. AKR1D1 splice variants were over-expressed in HEK293 cells, and incubated with cortisol, dexamethasone or prednisolone. *AKR1D1-002* over-expression resulted in rapid cortisol clearance (as measured by liquid chromatography-mass spectrometry). However, the clearance of the synthetic glucocorticoids, dexamethasone and prednisolone, was much more limited. Consistent with these data, GR activation, as measured by a luciferase-reported assay, was decreased in cortisol-treated *AKR1D1-002* over-expressing cells, in comparison with empty vector controls. However, no differences in GR activation were observed in *AKR1D1-002* over-expressing cells, when treated with dexamethasone and prednisolone. In contrast to *AKR1D1-002*, over-expression of either *AKR1D1-001* or *AKR1D1-006* had no effect on cortisol clearance. However, AKR1D1-001 significantly decreased GR activation following dexamethasone and prednisolone treatment, suggestive of increased clearance of synthetic glucocorticoids. AKR1D1-006 failed to regulate GR activation, following either natural or synthetic glucocorticoid treatment. Through genetic manipulation of expression of AKR1D1 splice variants, we have demonstrated their differential ability to regulate natural and synthetic glucocorticoid metabolism. Our data suggest that, while AKR1D1-006 may be functionally inactive, the AKR1D1-001 isoform may have an important role in regulating exogenous glucocorticoid availability. This might have implications for patients being treated with synthetic glucocorticoids and their risk of developing adverse metabolic side effects.

DOI: 10.1530/endoabs.65.P171

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Physicochemical optimization of dermal insulin patches: effects on selected metabolic parameters in STZ-induced diabetic rats

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Investigations conducted in our laboratory have shown that transdermal delivery of insulin has several potential advantages over the conventional route. These pectin-insulin (PI)-containing dermal patches possess the ability to maintain sustained controlled release of insulin into the bloodstream of streptozotocin-induced diabetic rats with concomitant reduction of blood glucose levels. We have successfully formulated and optimized the concoction of the PI-containing dermal patch which exhibited improved therapeutic efficacy in glycaemic control mediated by prolonged plasma insulin concentrations in the therapeutic range. Previous studies have shown that the PI-containing dermal patch formulation (33.60 μg/kg) derived from a combination of two 16.80 μg/kg patches prepared with 4 g of pectin is the optimum and chemically stable dermal formulation. Accordingly, the current study was designed to evaluate the chronic treatment of the optimized PI-containing dermal patch on selected metabolic parameters in separate groups of STZ-induced diabetic rats. Dermal patches containing 4 g of pectin and a total insulin concentration of 33.60 μg/kg were formulated by dissolving pectin/insulin in deionised water with subsequent solidification with $CaCl_2$. Animals were treated twice daily 12 h apart for the 5-week experimental period. Blood glucose concentrations and physical parameters (food and water intake, urine output and body weight) were measured weekly. Blood samples were collected for insulin, glycated haemoglobin and antioxidant activity determination. Our findings show that the optimized PI-containing dermal patch reduces blood glucose concentrations with concomitant increase in plasma insulin concentrations. Furthermore, glycated haemoglobin levels were significantly reduced and endogenous antioxidant enzyme activity was increased as a result of improved glycaemic control. The findings of the current study suggest that the PI-containing dermal patch formulation has improved therapeutic efficacy in the alleviation of diabetes mellitus and associated complications. These findings are of significant importance as the PI-containing dermal formulations can be developed into unit dosage forms with prolonged therapeutic efficacy.

DOI: 10.1530/endoabs.65.P172

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Effect of maternal obesity on offspring metabolic indices

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Maternal obesity is associated with altered metabolic function in the offspring, but its age and sex-specific metabolic effect not clearly defined. Female adult Sprague–Dawley (SD) rats were fed an obesogenic diet – high fat diet of 7.76 kcal/g (experimental group) or standard rat chow (3.52 kcal/g, control group) for 8 weeks prior to mating and throughout gestation and lactation. Proven fertile male SD rats were used for mating. Male and female offspring were weaned onto standard rat chow on postnatal day (PND) 21 until PND 90. Body weight and fat mass were determined in the offspring. Rats were sacrificed, and blood collected on PND 30 (juvenile) and PND 90 (adulthood) to determine glucose, insulin and leptin levels. Despite no difference in postnatal body weight, male offspring of obese dams had a higher fat mass on both PND 30 and 90 ($P<0.05$) relative to control offspring. Maternal obesity had no effect on glucose level on PND 30 but induced hyperglycaemia in both male and female offspring on PND 90 ($P<0.05$) when compared with control offspring. Only male offspring of obese dams exhibited a higher insulin level on both PND 30 and 90 ($P<0.05$) compared with offspring of control dams. Serum leptin did not vary in either male or female offspring of control and obese dams. The data suggest that maternal obesity may cause age-dependent alterations in glucose homeostasis and may also have a gender-specific effect on adiposity and insulin secretion in the offspring, with males more likely to be predisposed to overweight and diabetes.

DOI: 10.1530/endoabs.65.P173

P174

Impact of free fatty acid 4 receptor internalization on signalling

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The free fatty acid 4 receptor (FFA4R) is highly expressed in adipose tissue and other tissues that are involved in metabolic homeostasis, where its pharmacological stimulation improves glucose uptake and insulin sensitivity. Work by our and other groups have revealed that, contrary to textbook knowledge, GPCRs are not only active at the plasma membrane, as previously believed, but also at intracellular sites such as early endosomes or the Golgi complex/trans-Golgi network. However, the relevance of this phenomenon for signalling by FFA4R and other metabolically relevant GPCRs is presently largely unknown. Here, we used highly inclined and laminated optical sheet (HILO) microscopy and bioluminescence resonance energy transfer (BRET) to elucidate the relationship between FFA4R short isoform internalization, trafficking and signalling. Our results indicate that the FFA4R rapidly internalizes to early endosomes upon stimulation with the full agonist TUG-891. Subsequently, the FFA4R was found to recruit mini $G\alpha_{i/o}$ protein probes to membranes of early endosomes, indicating that the FFA4R remains active in this compartment after internalization. Further experiments are under way to investigate the consequences of FFA4R endosomal signalling downstream of G protein activation and its implications in adipocyte metabolism. Understanding the mechanisms and relevance of endosomal signalling by FFA4R and other metabolic GPCRs could ultimately pave the way to novel therapeutic strategies for diabetes and other metabolic diseases.

DOI: 10.1530/endoabs.65.P174

P175

The effect of tumour necrosis factor-alpha on myogenesis in immortalised human myoblasts

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Skeletal muscle exists in a state of continuous synthesis and breakdown of muscle proteins in order to preserve normal metabolic and locomotive functioning. Hormones are well established regulators of this homeostatic process. Chronic systemic inflammation can dysregulate skeletal muscle homeostasis via the disruption of endocrine signalling pathways. This can result in skeletal muscle atrophy, which is strongly implicated in the pathogenesis of type 2 diabetes and

sarcopenia. Improving our understanding of the mechanisms underlying this process is therefore important in order to develop novel pharmacological agents capable of preventing skeletal muscle mass loss and disease progression. We have subsequently developed a cell model that simulates this pro-inflammatory state *in vitro* utilising immortalised human myoblasts (LHCN-M2). We demonstrate that treatment of LHCN-M2 cells with the pro-inflammatory cytokine tumour necrosis factor alpha (TNFα) decreases myoblast proliferation and myotube formation in a dose-dependent manner. The addition of 10 ng/ml, 20 ng/ml and 30 ng/ml TNFα to LHCN-M2 myoblasts for 48 h decreased cell proliferation by 16%, 22% and 31% respectively ($r = -0.778$, $n = 32$, $P < .001$). Similarly, the addition of 2.5 ng/ml, 5 ng/ml and 10 ng/ml TNFα to myoblasts after 7 days of differentiation for 72 h decreased myotube formation by 47%, 59% and 97% respectively ($r = -0.911$, $n = 26$, $P < .001$). We also show that it is possible to pharmacologically modulate the anti-proliferative activity of TNFα, providing a platform for the screening and identification of novel therapeutic avenues to prevent or treat skeletal muscle atrophy.

DOI: 10.1530/endoabs.65.P175

P176

Brain derived neurotrophic factor (BDNF) methylation in patients with impaired glucose regulation: implications progression to type 2 diabetes mellitus (T2DM)

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Introduction

There is growing evidence of external factors modulating epigenetic modifications and their contribution to the development of obesity and T2DM. One of the epigenetic signatures is DNA methylation. We investigated whether a lifestyle intervention could influence DNA methylation of Brain derived neurotrophic factor (BDNF) in individuals with IGR, as BDNF is thought to play an important role in glucose metabolism.

Methods

IGR participants ($n = 20$) were recruited and underwent anthropometric measurements/fasting blood tests and adipose tissue biopsy pre/post-lifestyle (6 months) intervention. Genomic DNA was extracted from adipose tissue, bisulphite converted and pyrosequencing was used to determine methylation levels in the IV exon of the BDNF gene.

Results

The intervention did not result in differences within the 4 CpGs methylation (comparing baseline and after intervention). However we found positive Pearson correlations at the baseline between CpG1 and weight ($r = 0.462$, $P = 0.04$); CpG1 and hip–waist ratio ($r = 0.494$, $P = 0.027$); also negative correlations between CpG3 and BMI ($r = -0.886$, $P = 0.003$); and CpG3 and triglycerides levels ($r = -0.536$, $P = 0.022$). Considering those patients who lost 3% or more of weight after intervention, we found a negative correlation at baseline between CpG3 and BMI ($r = -0.707$, $P = 0.05$). Considering the data after the intervention we found a positive correlation between CpG2 and insulin levels ($r = 0.590$, $P = 0.006$). Regarding those individuals who lost 3% of weight or more we found a positive correlation between CpG3 and HOMAS ($r = 0.802$, $P = 0.05$); and negative correlation between CpG4 and HOMAB ($r = -0.869$, $P = 0.05$).

Conclusion

Observed associations between BDNF DNA methylation patterns across different glucose metabolic states suggest that BDNF may be involved in the pathophysiological process of insulin resistance and type 2 diabetes.

DOI: 10.1530/endoabs.65.P176

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Investigating the role of GPR119 in the vagus nerve

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The prevalence of obesity and its associated metabolic diseases are increasing, but current treatments are ineffective or impractical. Understanding how the gut–brain axis senses nutrients to regulate appetite and glucose homeostasis may identify new drug targets and treatments. The G protein-coupled receptor 119 (GPR119) has several endogenous lipid ligands and has been proposed to act as a nutrient sensor in the gastrointestinal tract. GPR119 is expressed on enteroendocrine cells and pancreas, and has been shown to have beneficial effects on glucose homeostasis, at least in part because it can stimulate the release of incretins. It has also been found to suppress food intake, making GPR119 a potential target for type 2 diabetes treatments, though to date synthetic ligands have proved largely ineffective. Understanding how GPR119 can regulate energy and glucose homeostasis may facilitate better drug design and targeting. The vagus nerve permits neuronal signalling between the gastrointestinal tract and brainstem, and playing an important role in appetite regulation. GPR119 has recently been found to be expressed in the nodose ganglia (NG), where the cell bodies of vagal afferent neurons reside. Our data show that murine GPR119 is highly expressed in both the left and right NG compared to gastrointestinal tract tissues (duodenum, jejunum, ileum, and colon). However, fasting did not significantly alter GPR119 expression in any tissues examined. *In vitro* cultured murine NG cells were treated with the endogenous GPR119 ligand, oleoylethanolamide (OEA, 10 mM) or the synthetic GPR119 ligand, AR231453 (400 nM). Both agonists increased intracellular calcium mobilization in NG cells. However, oral gavage of 30 mg/kg OEA did not alter the response to a glucose tolerance test or influence food intake in mice. Further work is required to determine whether other GPR119 ligands may influence metabolic regulation through the vagus nerve, and whether these systems represent useful therapeutic targets.

DOI: 10.1530/endoabs.65.P177

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Glycaemic response to a mixed meal challenge: does camel milk preload confer an advantage?

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Camel milk provides a modest portion of the overall global milk share but is an important source of protein in arid regions. Perceived health benefits include anti-diabetic properties attributed to its unique composition. We hypothesise that exogenous insulin present in camel milk mediates a hypoglycaemic effect. In a randomised, double blind crossover study, eleven normoglycaemic individuals were allocated to receive a 300 kcal pre-load of camel milk or cow milk ten minutes prior to ingestion of a 500 kcal protein and carbohydrate mixed meal. Samples for glucose, insulin and c-peptide were taken at intervals over four hours. Data presented as mean ± SD. Baseline glucose in both groups was comparable ($P = 0.75$). Compared to camel milk, cow milk preload caused a significant rise in plasma glucose ($P < 0.001$). Glucose in both the cow milk and camel milk groups start to drop after a peak at $t = 25$ min (6.83 ± 0.36 mmol/l cf. 6.45 ± 0.31 mmol/l). Glucose levels in the camel milk group return to baseline at t = 180 min. In the cow milk group there is a period of relative hypoglycaemia (−0.7 mmol/l) compared to baseline which persists beyond termination of the study period. There was no significant difference between baseline insulin in both groups ($P = 0.54$). Peak insulin or insulin area under the curve (AUC) did not differ between the two groups ($P = 0.11$ and 0.94 respectively). Furthermore, there was no significant difference in peak c-peptide levels or AUC between the two groups ($P = 0.23$ and $P = 0.32$ respectively). In this group of healthy volunteers, exogenous insulin does not appear to play a role as both milks elicit a comparable rise in insulin and c-peptide. Plasma glucose levels demonstrate less variability following camel milk preload compared to cow milk despite similar insulin values. Further study is required to investigate potential mechanisms for the difference in glucose profiles.

DOI: 10.1530/endoabs.65.P178

P179

Continuous subcutaneous insulin infusion (CSII): a trust-wide audit

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Aims and objectives
Continuous subcutaneous insulin infusion (CSII) has been in clinical practice since 1970s. NICE guidance (2008) recommends CSII in adults with type 1 diabetes (T1DM) if attempts to achieve target HbA1c with multiple daily injections (MDIs) result in disabling hypoglycaemia or HbA1c levels remain above 69 mmol/mol. The aim of our audit was to check compliance of our service against NICE guidance, and to see if CSII improved glycaemic control and/or hypoglycaemia in our patient cohort.
Methology
We conducted a retrospective audit of our adult pump service at West Suffolk NHS Foundation Trust. The service started in 2004. We considered the following audit parameters: Type of diabetes, indication for commencement of CSII, HbA1c at baseline and over 11 years, change in hypoglycaemia and use of other technology.
Results
We have 14.5% (n:161) of our patients with T1DM on insulin pumps. All patients on CSII were confirmed to have T1DM and fulfilled NICE criteria for pump initiation and continuation. Most common indication was hyperglycaemia followed by hypoglycaemia, pregnancy, dawn phenomenon and diabetic gastroparesis. HbA1c showed sustained improvement over 11 years period. Disabling hypoglycaemia also showed significant improvement.
Conclusion
Our CSII audit indicates compliance with NICE 2008 guidance, and shows sustained improvement in overall glycaemic control over 11 year period. There is a need to expand our service to offer CSII to more women with T1DM and poor glycaemic control during pregnancy and preconception period.

DOI: 10.1530/endoabs.65.P179

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Very low calorie diet (VLCD) in obese patients with longstanding type 2 diabetes mellitus: real-world outcomes with twelve months follow-up

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Introduction
Recent randomised controlled trials have demonstrated the efficacy of very low calorie diets (VLCD) in carefully selected patients with type 2 diabetes mellitus (T2DM). However, there is paucity of evidence regarding the efficacy of VLCD in the real-world setting. We evaluated outcomes in obese T2DM patients who underwent VLCD at our institution.
Methods
This retrospective observational study included all patients who had undergone VLCD from August 2014 to December 2017 ($n=61$). The VLCD programme consisted of an eight-week 800 kcal/day dietary restriction (600 kcal meal replacements plus 200 kcal vegetable dish) accompanied by structured education. Metabolic parameters and medications were recorded at baseline, immediately post-VLCD, six and twelve months post-VLCD. The primary outcome was reduction in weight at twelve months post-VLCD.
Results
The mean age of patients was 55.2 years (range 36–75 years). The mean starting weight was 108.2 kg. There was a significant reduction in weight of 9.96 kg ($P<0.001$) immediately post-VLCD, with net weight loss sustained to twelve months ($P<0.05$). The mean starting body mass index (BMI) was 38.2 kg/m^2. There was a significant reduction in BMI sustained to twelve months ($P<0.05$). The mean starting HbA_{1c} was 79.60 mmol/mol. There was a significant reduction in HbA_{1c} of 13.29 mmol/mol immediately post-VLCD ($P<0.001$) which did not sustain at six or twelve months. 78.7% patients had a reduction in T2DM medication burden post-VLCD, sustained in 44.3% patients at twelve months. 6/23 (26.1%) patients who were on insulin pre-VLCD, no longer required it at twelve months. Analysis of patients with T2DM diagnosis duration >6 years demonstrated statistically significant weight loss sustained to twelve months ($P<0.001$).
Conclusion
To our knowledge, this is the first study reporting outcomes of VLCD in obese patients with a diagnosis of T2DM for >6 years. Our results demonstrate sustained reduction in BMI and weight, reduction in medication burden and temporary reduction in HbA_{1c}.

DOI: 10.1530/endoabs.65.P180

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The progesterone metabolite epiallopregnanolone sulphate induces glucose-stimulated insulin secretion from human and mouse islets and is reduced in gestational diabetes mellitus

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Serum concentrations of progesterone sulphates are raised in intrahepatic cholestasis of pregnancy (ICP), the commonest pregnancy-specific liver disease. Women with ICP have increased rates of gestational diabetes mellitus (GDM). We hypothesised that raised progesterone sulphates may modulate glucose homeostasis. Progesterone sulphates were assayed in serum samples from participants of the hyperglycaemia and adverse pregnancy outcomes (HAPO) study ($n=79$–94), and from women with GDM ($n=19$) matched with healthy controls ($n=39$), using ultra-performance liquid chromatography and mass spectrometry. Islets were isolated from female C57BL/6 mice or obtained from human organ donations. Static incubation was performed in both mice and human islets to assess insulin secretion in the presence of progesterone sulphates. As progesterone sulphates can bind the bile acid receptors, FXR and TGR5, islets were studied from Fxr$-/-$ and Tgr5$-/-$mice. Analysis of insulin was by radioimmunoassay. Serum samples from the HAPO study demonstrated significantly lower progesterone sulphates in women with higher fasting plasma glucose. Reductions were seen in PM3S, PM3DiS ($P<0.05$), epiallopregnanolone sulphate (PM5S) and allopregnanolone sulphate (PM4S) ($P<0.01$) and pregnanolone (PM6S) ($P<0.001$). Similarly, women diagnosed with GDM had reduced serum progesterone sulphate concentrations, in particular PM5S ($P<0.05$). In islets, 50 μM PM5S was shown to increase glucose stimulated insulin secretion by at least 2-fold in both mouse and human islets at 20 mM glucose concentrations ($P<0.001$). This effect was not abolished from islets obtained from Fxr$-/-$ or Tgr5$-/-$ mice. In conclusion, progesterone sulphates are reduced in the serum of women with GDM and increase glucose stimulated insulin secretion. This is not mediated by Fxr or Tgr5. The increased rate of GDM seen in ICP women could be linked to progesterone sulphate mediated insulin release.

DOI: 10.1530/endoabs.65.P181

P182

Oral chenodeoxycholic acid increases post-prandial anorectic gut hormone levels and increases indices of insulin sensitivity

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Background
Increased circulating bile acids may contribute to improved glucose control and augmented secretion of the gut hormones peptide tyrosine tyrosine (PYY) and glucagon-like peptide-1 (GLP-1) observed post-prandially in patients following bariatric surgery. Oral bile acids could represent a non-surgical means of improving glucose tolerance after a meal.
Aim
To investigate the effects of a single oral dose of ursodeoxycholic acid (UDCA) and chenodeoxycholic acid (CDCA) on glucose homeostasis and gut hormone secretion post-prandially.
Methods
In a randomised placebo-controlled cross-over study, twelve healthy volunteers ingested no bile acid, UDCA or CDCA at 13–16 mg/kg 60 min prior to consuming a milkshake meal (700 kcal). Peripheral blood samples were taken at intervals and gut hormones were assayed from plasma using radioimmunoassay or commercial ELISA kits. Area under the curve (AUC) was calculated using the trapezoid rule, with baseline as y = 0, and compared with repeated measures one-way ANOVA with Geisser–Greenhouse correction.
Results
Ingestion of either bile acid attenuated the post-prandial rise in insulin and was associated with an increase in PYY. CDCA was also associated with an increase in GLP-1 and a reduction in glucose dependent insulinotropic polypeptide (GIP).

	Nil	UDCA	CDCA
Glucose mmol/l·min	1487 (40.6)	1413 (52.5)	1453 (45.4)
Insulin μU/ml·min	9682 (1630)	7278 (1040)	6174 (883)*
Insulin: glucose ratio	1812 (273)	1406 (189)*	1228 (154)*
GLP-1 total pmol/l·min	1517 (243)	1596 (275)	2166 (332)**
PYY pmol/l·min	675.4 (131)	990.9 (176)*	1490 (299)*
GIP pmol/l·min	31693 (5000)	30774 (7320)	22128 (4460)*

Changes in Area Under the Curve (AUC) when compared with no bile acid; *$P<0.05$; **$P<0.001$

Conclusions

Before a meal, oral exogenous CDCA improves indices of insulin sensitivity and increases levels of GLP-1 and PYY. CDCA is a possible adjunctive treatment of treatment of type 2 diabetes and further trials are required.

DOI: 10.1530/endoabs.65.P182

P183

Hepatic effects of new anti-diabetic drugs: real world data from a retrospective study

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Background and aims

There is evidence that new anti-diabetic drugs may limit liver disease progression, reduce liver fat and normalize serum aminotranferase levels in patients with NAFLD. We compared the effectiveness of new drug classes on liver fat in T2DM patients by means of surrogate markers.

Materials and methods

In an observational retrospective study we analysed the 12-month time-courses of clinical and anthropometric data of T2DM cases treated by SGLT2-inhibitors ($n=131$), DPP4-inhibitors ($n=102$), and GLP-1R-agonists ($n=232$), alone or in combination with metformin/sulfonylureas, together with a group of 154 cases treated by GPs with sulfonylureas ± metformin and/or pioglitazone (CONT). The aminotransferase levels, the Fatty Liver Index (FLI-a validated measure of steatosis) and the Fib-4 score (a surrogate marker of fibrosis) were measured at 6-month intervals.

Results

In the whole population, mean BMI was 34.7 ± 7.0 kg/m^2, ALT levels 35.8 ± 24.8 U/l. A1c levels were higher in SGLT-2Is and GLP-1RAs compared to other classes. ALT levels were higher in GLP-1RA treated cases, and lower in DPP-4I-treated patients, compared to other classes. At 12-mo follow-up changes in ALT levels were present in GLP-1RA and SGLT-2I groups. At baseline most cases were classified as steatosis (89%) or indeterminate (9%) by FLI. In a logistic regression analysis, treatment with SGLT-2Is was the only therapy associated with significant improvement in FLI class from steatosis to indeterminate/no steatosis (15% of cases) (OR, 5.12; 95% CI, 1.50–17.5), after adjustment for age, gender, BMI, ALT and HbA1c at baseline. No significant changes in Fib-4 score were measured at follow-up in any group.

Conclusion

SGLT-2Is and GLP-1RAs are particularly effective in metabolic control, and are associated with improved liver enzymes and markers of steatosis in T2DM at 12-month follow-up, without any difference in fibrosis markers.

DOI: 10.1530/endoabs.65.P183

P184

Vitamin B12 deficiency leads to fatty acid metabolism dysregulation and increased pro-inflammatory cytokine production in human adipocytes and in maternal subcutaneous and omental adipose tissue

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Vitamin B12 (B12) is an essential micronutrient required for several metabolic reactions. Animal and clinical studies show that B12-deficiency is associated with metabolic syndrome. Given the key metabolic role of adipose tissue, we investigated whether B12 deficiency may affect triglyceride synthesis and lipid metabolism leading to adipose tissue inflammation. The AbdSc pre-adipocyte cell line (Chub-S7) and human AbdSc primary pre-adipocytes were differentiated under different B12 concentrations (25 pM, 100 pM, 1nM, 500 nM). Human Om, Sc-AT and blood samples were collected from 106 pregnant women at delivery. Serum B12 and relevant metabolic risk factors were measured. Gene expression was performed by q-RT-PCR, *de novo* triglyceride synthesis was quantified by radioactive tracing, ß-oxidation and palmitate-induced oxygen consumption rate was determined using the seahorse-XF analyzer. Adipocytes cultured in low-B12 conditions showed significantly increased expression ($P<0.01$) of triglyceride biosynthesis genes (ELOVL6,SCD,GPAT,LPIN1 and DGAT2), a significantly decreased expression ($P<0.01$)of ß-oxidation genes (FAT/CD36, CPT1-ß, ACADL, ECHS1 and ACAA2) and an increased expression ($P<0.01$) of pro-inflammatory cytokines (IL-1, IL-6,IL-8,IL-18,TGF-β,TNF-α and MCP-1). These data were also confirmed in the AT of B12-deficient pregnant women. Additionally, real-time fatty acid flux synthesis and fatty-acid-oxidation induced by palmitate were significantly altered ($P<0.05$) in B12-deficient adipocytes. Our data highlights that B12-deficiency has profound effects on adipocyte dysfunction, opening new insights into the pathogenesis of maternal obesity and the relevance of micronutrient supplementation for pregnant mothers.

DOI: 10.1530/endoabs.65.P184

P185

Endotoxin and adiposity as mediators of down-regulating the BRITE fat phenotype

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Background

The acquisition of brown-adipocyte-properties by white-adipocytes (BRITE-adipocytes) is an appealing-prospect to combat obesity and type-2-diabetes-Mellitus (T2DM). This may support counteracting the impact of inflammation and mitochondrial-dysfunction, which contribute to the obesity-pathogenesis. However, our previous-findings have shown that the gut-derived-inflammatory-agent endotoxin can increase the inflammatory-response in white-adipose-tissue impacted by obesity and T2DM, although its effect on the browning-process is unknown. Therefore, the objective of this study was to (1) investigate the *in-vitro*-effect of endotoxin on the browning-process in human-adipocytes; (2) define the expression of brown-fat-genes and inflammatory-genes in human-abdominal-subcutaneous (AbdSc) and omental (AbdOm) adipose-tissue-cohort (AT; $n=128$ female; age: 31.6 ± 0.63) to determine the influence of adiposity, AT-depot, inflammation and mitochondrial-function.

Methods

Human-primary-adipocytes were differentiated with or without Rosiglitazone, which promotes adipocytes-browning, with or without endotoxin (100 ng/ml). Differentiated-cells were treated with isoproterenol to induce UCP1. AbdSc and AbdOm AT-biopsies were collected with ethical-approval during elective-surgeries. RNA from both cultured-adipocytes and AT was extracted and gene-expression was quantified by qRT-PCR.

Results

Endotoxin significantly reduced the BRITE-phenotype in the Rosiglitazone-treated-cells by reducing the key-brown-fat-genes-expression UCP1 ($P<0.05$), CIDEA ($P<0.05$), ELOVL3 ($P<0.05$), PLIN5 ($P<0.05$), SLC27A2 ($P<0.05$). Furthermore, endotoxin reduced key-mitochondrial-gene-expression (FIS1, DRP1, OPA1, MFN2, $P<0.05$). In addition, adiposity was associated with significantly reduced-expression of the key-brown-fat-genes (≈40%, $P<0.05$) and there was strong negative-correlation between BMI and brown-fat-genes in AbdSc-AT and AbdOm-AT ($P<0.05$). As anticipated adiposity significantly-increased inflammatory-genes-expression: IL6, MCP1, TNFα, IL1ß (≈30%, $P<0.05$) in both AbdOm-AT and AbdSc-AT. Interestingly, there were negative-correlations between inflammatory-genes and brown-fat-genes in AbdOm-AT ($P<0.05$), and direct positive-correlation between mitochondrial and brown-fat-genes in AT ($P<0.05$).

Conclusions

Endotoxin appears to reduce the *in-vitro* BRITE-phenotype-capacity in adipocytes due to enhanced-mitochondrial-dysfunction and inflammation,

which is exacerbated with increasing adiposity. Taken together, subjects with obesity and T2DM would appear to have a reduced-capability to promote a BRITE-phenotype in WAT, as a means to reduce further weight-gain than lean non-diabetic-individuals.

DOI: 10.1530/endoabs.65.P185

P186

AKR1D1 (5β-reductase) deletion drives hepatic inflammation, fibrosis and tumour development *in vivo*

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The enzyme 5β-reductase (AKR1D1) catalyses an essential step in bile acid synthesis. In addition, it controls intra-cellular steroid hormone availability through hormone clearance. As disturbances in steroid hormones and bile acid metabolism have potent effects on metabolic health, we hypothesize that AKR1D1 may play a role hepatic lipid accumulation. We generated global AKR1D1 knockout mice (KO) alongside wild-type controls (WT). Mice were fed either normal chow (NC) or the American lifestyle induced obesity syndrome diet (ALIOS; 45% fat, 55% fructose: 45% glucose in H_2O), which replicates the clinical features of non-alcoholic fatty liver disease (NAFLD), for 52 weeks. AKR1D1 KO mice fed ALIOS had increased hepatic steatosis in comparison with WT mice (WT: 16.7 ± 3.3, KO: 21.7 ± 3.6 mg/g, $P < 0.005$). In addition, there was evidence of increased hepatic inflammation scores in male AKR1D1 KO mice on NC (1.6 vs. 1.1, $P < 0.01$), but not ALIOS. However, liver biochemistry was significantly elevated in AKR1D1 KO mice fed ALIOS in comparison with WT mice (ALT; WT: 140.7 ± 51.9, KO: 404.7 ± 171.4 U/l, $P < 0.05$. AST; WT: 136.7 ± 39.0, KO: 360.7 ± 121.7 U/l, $P < 0.05$). Endorsing observations in our rodent model, AKR1D1 knockdown experiments in human hepatoma cells increased mRNA expression and secretion of pro-inflammatory cytokines (IL1β, IL-6 and IL-8). Hepatic inflammation is a key driver of fibrosis. AKR1D1 KO mice fed ALIOS had increased hepatic fibrosis as quantified by sirius red staining (WT: $5.4 \pm 2.6\%$, KO: $10.0 \pm 4.9\%$, $P < 0.01$). Furthermore, it is well-established that advanced fibrotic metabolic liver disease increases the risk for the development of hepatocellular carcinoma (HCC) and AKR1D1 KO mice were more prone to tumour development (WT: 11.5%, KO: 42.1%, $P < 0.05$). Deletion of AKR1D1 in combination with dietary stress evokes increased hepatic triacylglycerol content and fibrosis, which could exacerbate the progression of NAFLD to NASH and potentially fuel development of HCC.

DOI: 10.1530/endoabs.65.P186

P187

Low B12 is associated with increased *de novo* synthesis of 'unsafe' fatty acids in the liver

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Background
Vitamin B12 (B12) deficiency is associated with obesity and was recently shown to trigger lipid accumulation in the adipose tissues and liver. The body is capable of synthesizing fatty acids (FAs) endogenously via *de novo lipogenesis* in the liver. However, dysregulated levels are associated with adverse consequences in subjects. We therefore assessed B12 regulation of *de novo* fatty acid synthesis and the profile of various FAs in hepatocytes.
Methods
Hep G2 cell line was cultured using custom-made B12 deficient EMEM media and seeded in four concentrations of B12 media such as 500 nM (control), 1000 pM, 100 pM and 25 pM (low) B12 until reaching 100% confluence. Oil Red O (ORO) staining, RT-qPCR and gas chromatography were employed to examine the effect of B12 deficiency on *de novo* synthesis and profile of FAs in hepatocytes.
Results
Hepatocytes in low B12 (25 pM) had more lipid droplets compared to control B12 (500 nM). The master regulator SREBF1 and enzymes of *de novo* FA synthesis (ACLY, ACC, FASN, ELOVL6 and SCD1) were increased under low B12. Total FA level was significantly higher in low B12 than control. Low B12 increased levels of SFAs, MUFAs, trans-FA and PUFAn-6/n-3 ratio but had no significant effect on PUFA-total compared to control. Among individual FAs, even chains such as palmitate (C16), stearate (C18) and oleate (C18:1 n-9) were higher and minimal levels of odd chains such as margaric acid (C17), heneicosylic acid (C21) and tricosylic acid (C23) that were also upregulated in low B12 than control.
Conclusion
Our study provides novel evidence that vitamin B12 deficiency (1) upregulates hepatic *de novo* FA synthesis dominated by SFAs, (2) increases levels of even-chain SFA (C12, C14, C16, C18), odd-chain SFA (C17, C21 and C23), MUFA (C18:1n-9 and C18:1 n-7), TFAs (C16:1t and C18:1t) and had no effect on PUFA-total compared to control.

DOI: 10.1530/endoabs.65.P187

P188

Insulin signalling in kidney podocytes: an information theoretic approach

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Glomerular podocytes are directly regulated by insulin (1) and podocyte insulin resistance is implicated in diabetic kidney disease. Information theory derived statistical measures can be used to quantify information transfer via cell signalling pathways (2). This novel approach takes into account cell-cell variation in responses and the impact that this noise has on information transfer but has not yet been applied to signalling in podocytes. Here we quantify the mutual information (MI) between insulin concentration and effects in podocytes as a measure of information transfer via insulin receptors (IR), and use this to address how features of the IR signalling network influence information transfer. To do so, human IR expressing podocytes (ABIR cells) were stimulated with insulin, prior to immunofluorescence staining of phosphorylated Akt, quantification by high content imaging, and calculation of MI between insulin and the response (I(pAkt;insulin)). Insulin caused the expected concentration and time-dependent increases in pAkt, but MI values were low (<0.5 Bits, irrespective of whether S473 or T308 phosphorylation was measured). Inhibition of PTEN and PTP1B (negative regulators of IR signalling) increased pAkt levels but did not increase I(pAkt;insulin). Akt-mediates negative feedback control of its own activation and Akt inhibition (GSK690693) reduced I(pAkt;insulin) values. Thus, by quantifying information transfer via podocyte IR we have found a) that individual podocytes are unreliable insulin sensors with most information lost through signalling, b) that population averaged measures of pAkt cannot be equated to information transfer and c) that Akt-mediated negative feedback can protect information transfer in this model.
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DOI: 10.1530/endoabs.65.P188

P189

The FreeStyle libre flash glucose monitoring system: how it has improved glycaemic control for people with type 1 diabetes (T1DM) in Eastern Cheshire, UK

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Introduction

Many people with type 1 diabetes continue to experience suboptimal glycaemic control. We now also know that often HbA1c levels are an inaccurate reflection of glycaemic patterns and variability. We describe here how the systematic use of the FreeStyle Libre flash monitor helped improve the glycaemic control of many people with type 1 diabetes.

Methods

We report the outcomes of 92 consecutive adults (18 years of age or more) with type 1 diabetes who have begun using the FreeStyle Libre flash glucose monitor in East Cheshire, UK. All users were provided education and support by the diabetes specialist nurses (DSNs) prior to initiation. An HbA1c of 60 mmol/mol was taken as the upper threshold for suboptimal glycaemic control.

Results

The mean cohort age was 43 years for men and 39 years for women (overall range 17–83 years). In 92 consecutive users, HbA1c decreased by an average of 10.7 mmol/mol (0.98%) after 3 months, and by 16.1 mmol/mol (1.47%) after 6 months. Crucially, there was also a narrowing of the distribution of HbA1c, with many fewer people (7 people at six months compared with 32 at baseline) crossing an HbA1c $\geq$80 mmol/mol (9.5%) (χ^2 3.2, $P<0.0001$). Neither the gender nor duration of diabetes impart any significant effect upon the changes in HbA1c. In multiple regression modelling, increasing age was associated with a lesser reduction in HbA1c at 6 months (beta = –0.289; $P=0.04$) independent of BMI and gender.

Conclusion

Flash glucose monitoring has great potential for improving both glycaemic control as well as quality of life for adults with type 1 diabetes. The technology provides significantly more data than the intermittent results obtained by traditional subcutaneous blood glucose monitoring, which may not capture intervals of extreme variability or relatively asymptomatic nocturnal events.

DOI: 10.1530/endoabs.65.P189

P190

Androgen receptor reduced sensitivity is associated with increased mortality, poor glycemic control and BMI in men with type 2 diabetes – a 14-year follow up study

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Introduction

Hypogonadism is associated with poorer glycaemic outcomes/increased all cause and cardiovascular morbidity/mortality in type 2 diabetes mellitus (T2DM). Increasing CAG repeat number within exon 1 of the androgen receptor gene is associated with increased androgen receptor resistance/insulin resistance. We here investigated the link between CAG repeat number and outcomes in T2DM men.

Methods

We determined in a long-term 14-year follow-up cohort of 274 T2DM Caucasian men in Salford UK, the association between baseline androgen status/CAG repeat number and metabolic trajectory/mortality. Baseline serum total testosterone was determined by tandem mass spectrometry and CAG repeats by PCR followed by Sequenom sequencing.

Results

Lower baseline total testosterone was associated with higher Body Mass Index (BMI)(kg/m^2) at 14-year follow-up: regression coefficient −0.30 (95% CI −0.445 to −0.157), $P=0.0001$ (total testosterone data). A higher baseline CAG repeat number associated with higher follow-up BMI in 2016 – each unit increase in CAG repeat associated with an increment of 0.43 in BMI 2016; and also higher HbA1c 2016. At an average 14 year follow-up 55.8% of hypogonadal men had died vs. 36.1% of eugonadal men ($P=0.001$). There was a 'u' shaped relation between the number of CAG repeats and mortality such that 21-23 CAG repeats was associated with an up to 58% lower mortality rate than <21 CAG repeats and >23 CAG repeats. Thus there was an optimal number of CAG repeats in relation to mortality rate. This relation was independent of baseline testosterone.

Conclusion

A higher number of CAG repeats at the testosterone receptor gene is associated with a higher future BMI/increased HbA1c. There was a 'u' shaped relation between CAG repeat number and mortality rate. A greater understanding of the interaction between CAG repeat number and circulating testosterone level may aid understanding of longer term health outcomes in men with T2DM.

DOI: 10.1530/endoabs.65.P190

P191

Male testosterone levels and laboratory practice: a need for a standardised approach to measurement and reporting

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Background

Diagnosis and treatment guidelines of men with adult-onset testosterone deficiency (TD) were published by the British Society for Sexual Medicine (2017). Laboratory practice has a major role in supporting these with accurate and precise total testosterone (TT) methods and standardised pre- and post-analytical protocols.

Objective

Our study investigated whether laboratory practice supported management guidelines of adult-onset TD.

Methods

A representative internet-based questionnaire-survey of senior laboratory scientists (UK/Republic of Ireland) was conducted (April–May 2018). Questions reflected sampling, general laboratory practice, reference ranges and reporting of results. The results were analysed in conjunction with data obtained from the National External Quality Assurance Service (UK NEQAS) on assay performance.

Results

Analyses of 96 questionnaires returned the following: 74 laboratories stated that optimal sampling time was communicated to users; 81 laboratories used immunoassays; 76 laboratories included reference ranges for adult men (31 had dual/multiple age-related intervals). Wide variability in lower/upper limits was evident in the common immunoassays; the majority of reference ranges were from manufacturers (50.0%) or historical (18.8%). Action limits based on TT levels were used by 64 laboratories, but 63 did not report a borderline range as suggested by guidelines. Protocols for cascading tests based on TT were evident in 58 laboratories, with 50 laboratories offering calculated free testosterone; Interpretative comments were provided by 67 laboratories, but no references were made to management guidelines. Data from UK NEQAS demonstrated considerable variation in testosterone assay performance.

Conclusions

Clinicians in all areas, and particularly in Primary Care, require clearer guidance from laboratories in the interpretation of androgen status in men. Our results

reinforce an urgent requirement for action regarding standardisation and harmonisation of testosterone assays and laboratory function.

DOI: 10.1530/endoabs.65.P191

P192

Lipoprotein(a) as a predictive biomarker for subclinical coronary atherosclerosis

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Background
Lipoprotein(a) (Lp(a)) is an independent, causal, genetic risk factor for cardiovascular disease (CVD). Coronary artery calcium (CAC), measured by computerised tomography (CT) scans, is a known marker for atherosclerosis. CT Agatston scores, also known as CAC scores, are thought to be better predictors of CVD than traditional risk factors. There is conflicting data regarding the relationship between Lp(a) levels and CAC. A preliminary study has suggested a positive association between Lp(a) and CAC scores within the United Kingdom population. Therefore, this study investigated the association between Lp(a) and coronary atherosclerosis, as measured by CAC, in a larger cohort. Traditional cardiovascular risk factors such as: diabetes mellitus and HbA1c levels, hypertension and smoking status as well as age and gender were also evaluated.
Methods
Data of 565 patients with recorded Lp(a) levels, CAC scores, age-and-gender-adjusted CAC percentiles and traditional cardiovascular risk factors were collected. Lp(a) levels <300 mg/l were considered normal. Patients were stratified according to CAC scores categorised into the following ranges: 0, >0–400, >400 and across CAC percentile ranges of: 0, 1–75%, >75%. Variables were compared across the whole population and specifically in Caucasians and Asian Indians. Chi-squared tests were conducted.
Results
There was no significant association between Lp(a) levels and CAC scores along with corresponding CAC percentiles in the whole population and Asian subgroup. In the Caucasian subgroup, a significant association ($P<0.05$) was found between Lp(a) levels and CAC scores but not for the corresponding CAC percentiles. CAC scores and CAC percentiles significantly differed ($P<0.05$) with age and gender. Traditional cardiovascular risk factors were significantly associated ($P<0.05$) with higher CAC scores.
Conclusion
Although Lp(a) may be a good predictive biomarker for subclinical coronary atherosclerosis, as measured by CAC, in Caucasians, it was not in Asians.

DOI: 10.1530/endoabs.65.P192

P193

Modulation of vagal afferent signalling by the amino acid metabolite sensor GPR35

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High dietary protein intake can suppress appetite, drive weight loss and improve glucose homeostasis. Understanding the mechanisms by which ingested protein is sensed may reveal new therapeutic targets for metabolic disease. G-protein coupled receptor 35 (GPR35) is activated by compounds including Kynurenic acid (Kyna), a product of amino acid metabolism. GPR35 is expressed in the intestines, most highly in the colon, and has recently been identified in the afferent vagus nerve, an important component of the gut–brain axis in the regulation of energy expenditure and glucose homeostasis. Interestingly, only a small number of post-prandial metabolite-recognising receptors have been identified in vagal afferents. GPR35 was the most abundantly expressed. We therefore investigated the effects of GPR35 agonists on vagal signalling. We confirmed GPR35 expression in both left and right nodose ganglia (NG) in mice. However, GPR35 expression was not changed in the NG or colon following a 24 h fast, in contrast to previously reported changes in other appetite-suppressing receptors (e.g. Y2-R). GPR35-like immunostaining was identified in epithelial cells in the mouse duodenum and colon, and in putative nerve axons in submucosal and muscular layers of duodenal and ileum slices. *In vitro* calcium imaging using cultured murine NG cells demonstrated that the GPR35 agonist Kyna modulates signalling in vagal neurons. Treatment with 15 uM Kyna or the synthetic GPR35 agonist Zaprinast, increased intracellular calcium mobilisation compared to non-GPR35 expressing HEK293 cells. Inositol phosphate-1 accumulation similarly increased post-treatment with Kyna, supporting likely GPR35-activation in a Gq-mediated manner. Further work is required to establish the physiological effects of GPR35 signalling in the vagus to determine whether this system mediates some of the beneficial effects of high protein diets.

DOI: 10.1530/endoabs.65.P193

P194

Efficacy of liraglutide in weight management post bariatric surgery patients: data from an Emirati cohort

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Introduction
Bariatric surgery (BS) is currently the most effective treatment for obesity. However, weight regain is a recognized challenge in post-surgical management. Drug treatment for weight regain after bariatric surgery has been used, but little published data is available on their efficacy. We have investigated the use of Liraglutide for relapse after BS in an Emirati population.
Methods
ICLDC patients with a previous history of bariatric surgery and a subsequent prescription of Liraglutide 3 mg formulation (Saxenda®), with a minimum follow-up period of 12 weeks were identified from the electronic database. SPSS 25 was used for statistical analysis. Data are presented as median (interquartile range).
Results
Full 12 weeks follow-up data were available on 132 patients (76.5% laparoscopic sleeve gastrectomy, 22% gastric bypass surgery and 1.5% gastric banding). Baseline characteristics are summarised in Table 1. At 3 months of follow up, weight was 90.7 (81.0–102.2) kg, accounting for a weight loss of 3.9 (1.5–6.8) % of the baseline weight. In 44 patients with type 2 diabetes, HbA1c dropped by 0.1 (-0.2 to 0.3) %. 79 patients from the initial cohort had 6 months follow-up data also available and showed a total weight loss of 4.9 (1.1–8.2) % from pre-liraglutide weight. Age, sex and type of BS had little or no effect on the weight loss following liraglutide therapy.
Conclusion
In the Emirati population studied, liraglutide treatment was efficacious as an adjuvant treatment modality for weight loss after bariatric surgery.

Table 1 Baseline Characteristics of the study population.

Demographic Variables	
N	132
Sex (male/female)	100/32
Type of surgery	101 LSG / 29 RYGB/ 2 LGB
Anthropometric Variables	**Median (IQR)**
Age	42.1(37.3–46.5) years
Weight	95.7 (83.9–106.0) kg
BMI	35.9 (33.1–39.0) kg/m^2

LSG: laparoscopic sleeve gastrectomy, RYGB: Roux-en-Y gastric bypass, LGB: laparoscopic gastric banding, IQR: interquartile range

DOI: 10.1530/endoabs.65.P194

P195

ISX-9 preferentially induces enterochromaffin and I-cell enteroendocrine lineages in human small intestinal organoids

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Enteroendocrine cells (EECs) are a hormone-/neurotransmitter-producing population with well-defined physiological roles. Knowledge regarding their differentiation program in the human gut, however, is scarce. Deciphering

endocrine specification could identify targets which allow the manipulation of specific EEC populations and form the basis for new treatments for metabolic, inflammatory and cognitive disorders. Isoxazole-9 (ISX-9) is a small molecule, previously used in protocols for neuronal and beta-cell differentiation. These cell types are developmentally similar to EECs and share lineage specification traits. In neuronal progenitors ISX-9 activates NeuroD1, a transcription factor that directs secretory differentiation in the gut. We explored the effect of ISX-9 on EEC identity in organoids derived from human tissue resident stem cells. ISX-9 promoted upregulation of NeuroD1, as expected, in addition to EEC progenitor marker Neurogenin 3 (Ngn3). Furthermore, an increase in the expression of Pax4, a known regulator of EEC differentiation in mouse, was also observed. Enterochromafin (chromogranin A (ChgA), TAC1, TPH1) and I-cell (cholecystokinin (CCK)) lineage markers were preferentially upregulated, whilst markers of other EEC lineages were either unaffected or down regulated. Immunostaining for ChgA and 5-HT and secretion assays confirmed functional enterochromaffin cell enrichment. An inducible Pax4-overexpressing human organoid model was generated to determine if this was sufficient to recreate the ISX-9 induced phenotype. Physiological levels of Pax4 expression recapitulated the phenotype exhibited by ISX-9. Interestingly high levels of expression inhibited all EEC differentiation and trapped cells in an early progenitor like state. These studies highlight the similarities between homeostatic mouse and human EEC specification and provides proof-of-concept that manipulating specific EEC cell populations is possible with small molecules. The potential to treat serotonin deficient diseases, eg depression by manipulating EEC cell fate is an attractive and novel supposition. Whether this can impact physiology and is translatable to the clinic remains to be determined.

DOI: 10.1530/endoabs.65.P195

P196

The differential effects of weight loss by RYGB versus very-low calorie diet (VLCD) on gut hormone levels and appetite: potential contribution to sustained weight loss

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Background
Roux-en-Y gastric bypass (RYGB) leads to effective and sustained weight loss whereas a Very-Low-Calorie diet (VLCD) is normally plagued by weight regain over time. Changes in gut hormones following each intervention may play a role. The aim of this study was to investigate gut hormone responses after 4 weeks of RYGB and VLCD.
Methods
We prospectively recruited 21 volunteers with obesity and type 2 diabetes undergoing RYGB, and a matched cohort of 22 volunteers who underwent a VLCD of 800 kcal/day for 4 weeks. A mixed meal test, with sampling for gut hormones, was administered before and after 4 weeks of the interventions. Subjective feelings of hunger, fullness and volume were recorded using Visual Analogue Scales (VAS).
Results
Weight losses following RYGB and VLCD at 4 weeks were similar at -10.3 ± 0.7 kg (-8.8 %) and -8.3 ± 0.6 kg (-7.6%) respectively. A drop in HbA1c of 8.4 ± 1.1 mmol/mol for surgery and 7.0 ± 0.8 for VLCD was observed. Post-prandial levels of GLP-1, PYY and Oxyntomodulin were augmented after RYGB, with significantly higher peak levels at 30 min after the meal, while ghrelin levels were reduced. In contrast, fasting ghrelin levels were increased after the VLCD whereas GLP-1, PYY, Oxyntomodulin and GIP remained unchanged. Fasted hunger and volume VAS scores were reduced while fullness scores were enhanced with surgery but were unaffected following the VLCD. After one year, RYGB subjects continued to lose weight (mean -29.5%) with a further drop in HbA1c (9.2 ± 1.3 mmol/mol). In contrast, VLCD subjects regained most of their initial weight loss (-1.9%) with their HbA1c back to pre-intervention level.
Conclusion
Anorectic gut hormones may play a key role in promoting the sustained weight loss in RYGB whereas the increase in ghrelin may contribute to the lack of sustained weight loss in VLCD.

DOI: 10.1530/endoabs.65.P196

P197

Immature β-cells are required for normal islet function and insulin release

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Background
A normal islet includes both mature and immature β-cells, with the former possessing higher insulin content and the latter displaying better proliferative capacity. However, it remains unknown whether immature β-cells also contribute to the regulation of insulin release, especially by commanding the activity of their mature counterparts.
Materials and methods
Pdx1, *Mafa*, and *Ngn3* were overexpressed in β-cells by either transduction with adenovirus (Ad-M3C) or using a doxycycline-inducible mouse line (*RIP7rtTA*$^{+/-}$; *TetO/M3C*$^{+/-}$ *(Tet-MAT))*. Conditional chemogenetic β-cell silencing was achieved in islets expressing the inhibitory DREADD h4MDi under the control of the *Ins1Cre* driver line (D-MAT). Confocal microscopy, coupled with biosensors or organic dyes, was used for measurement of Ca^{2+}, cAMP and ATP/ADP. HTRF assay was used to measure insulin secretion. RNAseq was performed using Lexogen QuantSeq 3' mRNA-Seq. Glucose tolerance was assessed by intraperitoneal glucose tolerance test.
Results
Pdx1 and *Mafa* expression levels were increased, while *Ngn3* showed no change. PDX1 and MAFA overexpression was largely restricted to PDX1^{LOW}/MAFA^{LOW} β-cells (defined as immature β-cells), and confirmed using Pdx1-BFP islets reporting historic cell PDX1 levels. Loss of immature β-cells presented with impaired islet Ca^{2+}, cAMP and ATP/ADP fluxes, as well as insulin secretion in response to glucose and/or Exendin-4. RNAseq analyses revealed dysregulation of gene pathways involved in carbohydrate and lipid analysis, and upregulation of transcripts involved in inhibitory signalling. Chemogenetic silencing in D-MAT islets showed that immature β-cells were dependent on islet Ca^{2+} signaling dynamics for their phenotype. Induction of immature β-cell loss *in vivo* by placing the Tet-MAT animals on doxycycline diet for 2 weeks resulted in glucose intolerance.
Conclusion
The current study redefines immature β-cells as a functionally competent, but islet-dependent β-cell subpopulation. Findings from single-cell screening studies or studies in dissociated cells should be interpreted carefully in light of differences arising from the islet context.

DOI: 10.1530/endoabs.65.P197

P198

Modulation of EGFR expression to increase islet transplantation success

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Background
Islet transplantation is an established treatment for type 1 diabetes mellitus. However, many recipients do not achieve independence from exogenous insulin since up to 50–70% of islets are lost post-transplant. An important factor determining transplant success is graft vascularisation. The epidermal growth factor receptor (EGFR) is a key pro-survival and proliferation factor. Here, we investigate for the first time if EGFR overexpression in pancreatic islets improves engraftment in an *in vivo* mouse model.
Methods
We generated adenovirus encoding human EGFR alongside a GFP reporter in order to overexpress this protein in primary tissue. Following successful infection

(as assessed by GFP expression), control (empty vector) or EGFR-infected islets were transplanted into the anterior chambers of the eyes of syngeneic mice ($n=12$ eyes randomly receiving either EGFR or control islets). Islet volume and blood vessel density/branching were assessed longitudinally over 30 days using confocal microscopy. To assess implantation, beta cell identity and function, expression of angiogenesis (eg VEGF), beta-cell enriched (eg Pdx1 and MafA) and beta-cell disallowed (eg Acot7 and LdhA) genes was determined by qPCR from identically infected islet groups (*in vitro*).

Results

Blood vessel density increased significantly over 30 days for both groups of islets ($P<0.05$), with EGFR-overexpressing islets demonstrating greater density compared to control islets at 30 days. qPCR results showed that EGFR-overexpressing islets had increased gene expression of angiogenic factors. Furthermore, consistent with preserved beta cell identity, beta-cell enriched factors were upregulated compared to control islets, while beta-cell disallowed genes were further repressed.

Conclusion

This is the first study to demonstrate that EGFR overexpression can promote the vascularisation of transplanted pancreatic islets *in vivo*. The transcriptional profiling of these islets also suggests an improved potential for beta-cell regenerative capacity and function. Further studies are underway to fully investigate the therapeutic potential of this intervention.

DOI: 10.1530/endoabs.65.P198

P199

Systemic and femoral adipose tissue-specific nontargeted plasma metabolome during acute hypercortisolaemia

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Background

Glucocorticoids have pleiotropic metabolic functions and acute glucocorticoid excess causes dramatic disruption of human metabolism. Whether glucocorticoids exert adipose tissue depot-specific effects on the nontargeted metabolome in unknown.

Aim

Assess the nontargeted metabolome in the systemic circulation and in femoral adipose tissue-specific blood samples in response to physiological hyperinsulinaemia and acute hypercortisolaemia.

Methods

Nine healthy male volunteers were studied on two occasions, after a hydrocortisone infusion (0.2 mg/kg per min for 14 h) and a saline infusion, given in randomized double-blind order. The subjects were studied in the fasting state and after a 75-g glucose drink with collection of systemic and femoral adipose tissue-specific plasma samples using the arteriovenous difference technique. Mass spectrometry–based nontargeted plasma metabolome analysis was performed and analysed by applying univariate analysis after normalization to total peak area per sample.

Results

Acute hypercortisolaemia induced significant changes in most classes of metabolites assessed, with similar trends across the systemic and adipose tissue-specific circulation; however, we observed a mean 2.3-fold increase of sphingolipids in the systemic circulation whilst the femoral adipose tissue did not respond to the stimulus. Acute hypercortisolaemia and hyperinsulinaemia had opposite effects on the output of fatty acids, sphingolipids and components of the tyrosine metabolism in the systemic circulation, with a significant increase in the first and a decrease in the second. Acute hypercortisolaemia also promoted increased release of acylcarnitines, fatty acids and oxidised fatty acids from the femoral adipose tissue, with an opposite effect of hyperinsulinaemia following oral glucose load.

Conclusions

We provide first-time evidence that acute hypercortisolaemia induces significant changes in the nontargeted plasma metabolome of the systemic and the femoral adipose tissue circulation. Our observations shed light on the effects of hypercortisolaemia in humans and may point to novel therapeutic targets to counteract the detrimental consequences of cortisol excess.

DOI: 10.1530/endoabs.65.P199

P200

A role for kisspeptin in long-term islet function in females

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Although characterised predominantly for its role in the brain, the neuropeptide kisspeptin has previously been shown to potentiate glucose-stimulated insulin through its receptor, GPR54; expressed abundantly in β-cells. We have previously reported a physiological role for kisspeptin signalling in the islet adaptation to pregnancy, using a β-cell specific GPR54 knockout mouse line (βGPR54ko). The aim of the present study was to examine the effects of impaired β-cell kisspeptin signalling on glucose homeostasis with aging in males and females using the βGPR54ko model. Male and female βGPR54ko and control (con) mice were fed chow (CD) or high-fat high-sugar diet (HFHSD) from 12 weeks of age. At 18 weeks, intraperitoneal glucose tolerance tests (IPGTT) and intraperitoneal insulin tolerance tests (IPITT) were carried out on all mice. IPGTT and IPITT were repeated 8 weeks later and every subsequent 4 weeks. At 18 weeks, HFHSD male and female mice had impaired glucose tolerance compared to CD ($P<0.001$), however, there was no significant difference between con and βGPR54ko mice (males: $P=0.5$, females: $P=0.4$). By 38 weeks, glucose tolerance in βGPR54ko HFHSD females was significantly impaired compared to HFHSD con mice (AUC con: 1919 vs. βGPR54ko: 3463; $P=0.0017$). This effect in βGPR54ko mice was not seen in HFHSD males ($P=0.4$). At subsequent time points HFHSD βGPR54ko females continued to exhibit impaired tolerance compared to equivalent controls ($P=0.039$), whilst no significant differences were observed in males ($P=0.3$). HFHSD significantly reduced insulin sensitivity in both males and females, as assessed by IPITT (week 38; males: $P=0.03$, females: $P=0.006$), but β-cell GPR54 knockout had no effect at any age (week 38; males: $P=0.09$, females: $P=0.6$). These results suggest that endogenous kisspeptin acting on the β-cells plays a physiological role in maintaining healthy glucose homeostasis with age in females, but that this role is less significant in males.

DOI: 10.1530/endoabs.65.P200

P201

Vitamin D-binding protein is required for the maintenance of α-cell identity and function

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Aim

Vitamin D-binding protein (DBP), also known as GC-globulin, transports vitamin D metabolites and is also a major actin scavenger. While DBP serum levels, gene polymorphisms and autoantigens have been associated with diabetes risk, the underlying mechanisms remain unknown. DBP is produced by the liver, but has recently been shown to be highly expressed in pancreatic α-cells. We therefore sought to investigate the role of DBP in α-cell identity and function using mice globally deleted for DBP ($DBP^{-/-}$).

Results

25(OH)D levels were low in $DBP^{-/-}$ mice, although no signs of vitamin D deficiency were present. Metabolic phenotyping revealed normal glucose tolerance but increased insulin sensitivity in $DBP^{-/-}$ animals compared to $DBP^{+/+}$ littermates, despite similar body weights. $DBP^{-/-}$ islets showed loss of glucagon secretion in response to low glucose and epinephrine, although total glucagon content was unaffected. While α-cell mass was normal following loss of DBP, morphometric analysis showed an ~30% decrease in α-cell size, which was associated with an increase in cell number. Suggesting changes in α-cell differentiation status, mRNA levels for *Pax6*, *Arx*, and *Pou3f4* were decreased by 2-fold in islets from $DBP^{-/-}$ mice. Multicellular Ca^{2+} imaging of $DBP^{-/-}$ islets revealed impaired recruitment of α-cells by low glucose or epinephrine, but an increase in basal β-cell Ca^{2+} fluxes. Examination of the α-cell cytoskeleton revealed increased F-actin fiber thickness and density with decreased G-actin levels. Upon super-resolution analysis, single glucagon granules were found to be smaller and more diffusely scattered in $DBP^{-/-}$ vs. $DBP^{+/+}$ islets, suggestive of defective maturation and/or trapping at the membrane. In sections from donors

with type 1 diabetes, DBP expression was more heterogeneous compared to normal donors, with high and low DBP-expressing α-cells being present.
Conclusion
DBP is a critical regulator of α-cell phenotype and function, with implications for diabetes therapy and diagnosis.

DOI: 10.1530/endoabs.65.P201

P202

Endoplasmic reticulum stress directly impacts mitochondrial function in human adipocytes

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Background
Dysfunctional endoplasmic reticula (ER) and mitochondria contribute to the pathogenesis of obesity and type 2 diabetes mellitus (T2DM). This may, in part, be facilitated by cross-talk between the two organelles during conditions of nutrient excess such as obesity, however the potential impact of ER stress on mitochondrial function has not been well studied. This study investigated whether induction of ER stress in human adipocytes may contribute to mitochondrial dysfunction.
Methods
Differentiated human adipocytes from a cell line (Chub-S7) and primary abdominal subcutaneous (AbdSc) adipocytes from lean and obese donors were treated with Tunicamycin (Tn) to induce ER stress. Mitochondrial function was assessed via oxygen consumption rate (OCR), mitochondrial membrane potential (MMP), ATP concentration, mitochondrial dynamics and number.
Results
Tunicamycin-induced ER stress increased respiratory capacity in a dose- and time-dependent manner (24 h:23%, ($P<0.05$); 48 h:68%, ($P<0.01$); 72 h:136%, ($P<0.01$)), with a preference for glycolysis after 72 h. Both ATP production and MMP were impaired in a corresponding manner (26%, $P<0.001$; 32%, $P<0.0001$ respectively), demonstrating that ER stress contributes to impaired mitochondrial function. Confocal microscopy highlighted that ER stress also resulted in reduced mitochondrial elongation (16%, $P<0.05$) and cellular area occupied by mitochondria (28%, $P<0.05$). Additionally, pDrp1, a key fission protein was significantly increased with Tn treatment. AbdSc adipocytes from lean subjects had a similar response to ER stress, with a 21% rise in OCR with Tn treatment ($P<0.01$), whilst adipocytes from obese subjects had a 33% reduced basal respiration than their lean counterparts ($P<0.001$), demonstrating an existing significantly impaired respiratory function.
Summary
These data suggest that ER stress induces mitochondrial dysfunction and that this is exacerbated during obesity, contributing to metabolic pathologies such as T2DM. This highlights that therapies targeting ER stress in adipocytes may be beneficial in the treatment of chronic ER stress and mitochondrial dysfunction in metabolic disease.

DOI: 10.1530/endoabs.65.P202

P203

The track-pump study

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Background
'Glycaemic tracking' describes the stability of HbA1c over time commonly observed in individuals with type 1 diabetes (T1DM). Preliminary studies have noted the relationship between early metabolic control and long-term outcomes, while recent evidence has been presented for glycaemic tracking in a large number of newly diagnosed individuals with T1DM. The benefits of tight glycaemic control, in terms of reducing microvascular complications and lowering HbA1c, are well reported. Insulin pump therapy may be used to achieve this strict glycaemic control more effectively.
Aims
To investigate if the phenomenon of glycaemic tracking occurs in a cohort of people with T1DM. To analyse the effect of insulin pump therapy on tracked HbA1c levels.
Methods
HbA1c readings were collected retrospectively for 160 patients on insulin pumps at Charing Cross Hospital. Statistical analyses were undertaken to compare yearly median HbA1c for the ten years surrounding inception of pump use. Pre- and post-pump median HbA1c were compared for paired data sets of varying time frames. HbA1c was plotted against time in 90-day intervals, and linear regression performed to model this relationship.
Results
The only significant ($P<0.0001$) difference in annual median HbA1c was found between the values from one year either side of the pump date. For all time frames analysed, there was a significant reduction in median HbA1c and IQR/median ratio following pump inception. Regression modelling of pre- and post-pump HbA1c values demonstrated a 4.4 mmol/mol lower Y-intercept at pump inception and a significantly more stable gradient ($P=0.0004$) post-pump.
Discussion
This study provides supportive evidence for glycaemic tracking in T1DM. Our results suggest that insulin pump therapy results in an incremental improvement in glycaemic control and a reduction in HbA1c variability. Larger-scale, prospective studies are needed to test this hypothesis further, and analyse the relationship between the timing of intervention and HbA1c trajectory.

DOI: 10.1530/endoabs.65.P203

P204

Glucocorticoid regulation of the PEPITEM pathway

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Dysregulated recruitment of leukocytes across endothelial cells into target tissues is a hallmark of the pathology of most chronic inflammatory diseases (CIDs). We have identified a novel homeostatic pathway that regulates T-cell migration during inflammation. The pathway is impaired in patients with CIDs such as type-1-diabetes and rheumatoid arthritis (RA), and is also attenuated in the elderly. The dysregulation of this pathway across all conditions is caused by a lower level of adiponectin receptors (AdipoRs) on B-cells, which leads to less secretion of PEPITEM (PEPtide Inhibitor of Trans-Endothelial Migration) in response to adiponectin. It is therefore important to understand how this pathway is regulated to potentially develop therapies that will re-balance T-cell recruitment during inflammation. We hypothesise that changes in AdipoRs expression on B-cells is caused by a common process across these distinct CIDs. Here, we aimed to determine whether glucocorticoids such as cortisol and their associated modulating enzymes, 11β-hydroxysteroid dehydrogenase 1 and 2 (11β-HSD1 and 2), regulate the PEPITEM pathway. Isolated B-cells were cultured in the presence of cortisol and other leukocytes for 48 h and the expression of AdipoR1/2 was measured using flow cytometry. Expression of 11β-HSD1/2, AdipoR1/2, and glucocorticoid associated genes was measured using qPCR. We observed up-regulation of AdipoR1/2 on B-cells in the presence of cortisol and monocytes but not on B-cells alone. In addition, we observed a reduction in the expression of AdipoR1/2 in the 11β-HSD1 knock-out mouse. The expression of 11β-HSD1 is very low in B-cells but is increased in the presence of stimulatory signals such as Interleukin-4. Our preliminary data indicate that patients with RA have lower expression of 11β-HSD1 than in gender and age-matched healthy controls. Our data indicate a potential role of cortisol in the regulation of the PEPITEM pathway via a cross-talk with monocytes and a potential role for 11β-HSD1.

DOI: 10.1530/endoabs.65.P204

P205

The American lifestyle induced obesity syndrome diet (ALIOS) in rodents recapitulates the clinical features and sexual dimorphism of NAFLD and NASH

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Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of metabolic syndrome, ranging from simple steatosis to the necro-inflammatory disease, non-alcoholic steatohepatitis (NASH). Development of NASH subsequently increases risk of hepatocellular carcinomas (HCC). Alongside the impact on the liver, NASH is associated with other clinical features, including insulin resistance, hyperlipidaemia and sarcopaenia. We demonstrate that mice fed the American lifestyle induced obesity syndrome diet (ALIOS) recapitulate many of the clinical characteristics of human NAFLD and NASH, making it a robust model for studying the condition. Male and female C57BL/6 mice were fed either normal chow (NC) or ALIOS (45% fat [30% trans-fat], 55% fructose: 45% glucose in H_2O; $n=15$ in each group) for 52 weeks. ALIOS fed mice had increased body mass and were insulin resistant. Relative quadriceps mass was decreased in ALIOS fed mice, mirroring sarcopaenia observed in NAFLD patients. In addition, metabolic caging revealed that ALIOS fed males were more sedentary than females. Plasma cholesterol, AST and ALT progressively increased in mice fed ALIOS in both sexes over the duration of the study. Whilst the ALIOS diet initially increased hepatic triglyceride content, by 52 weeks, hepatic triglyceride decreased (Males; NC: 21.7 ± 1.2, ALIOS: 16.7 ± 1.1 mg/g. Females; NC: 18.5 ± 0.7, ALIOS: 13.2 ± 0.8 mg/g, $P<0.05$). ALIOS induced liver inflammation in both sexes and was associated with increased hepatic fibrosis (Male; NC: 3.2 ± 0.5, ALIOS; $5.4\pm0.9\%$. Female; NC: 2.7 ± 0.8, ALIOS: $5.9\pm1.1\%$, $P<0.05$). Advanced fibrotic liver disease increases the risk of HCC; ALIOS fed male mice were more prone to tumour development (NC: 7.7%, ALIOS: 22.2%, $P<0.05$), while there was no incidence of macroscopic tumours in females. The ALIOS diet in mice recapitulates many of the clinical features of NAFLD and represents a robust and reproducible model for investigating the pathogenesis of NAFLD and its progression to NASH and HCC.

DOI: 10.1530/endoabs.65.P205

P206

Role of palmitoylation on GLP-1 receptor responses in pancreatic beta cells

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We have previously described how signaling responses for the glucagon-like peptide-1 receptor (GLP-1R), a class B GPCR that plays key roles in metabolic regulation and is a prime type 2 diabetes (T2D) target, are modulated by intracellular membrane trafficking. We have also recently shown that binding to the therapeutic GLP-1R agonist exendin-4 (Exenatide) triggers increased clustering and segregation of biologically active GLP-1Rs into cholesterol-rich plasma membrane nanodomains that enable compartmentalization of acute receptor signaling and clathrin-mediated endocytosis. Both disruption of plasma membrane microarchitecture via cholesterol depletion and mutation of cysteine 438 GLP-1R single palmitoylation site have a substantial impact on acute GLP-1R signaling and endocytosis. Downstream effects on insulin secretion from pancreatic beta cells indicate that these processes are relevant to GLP-1R physiological actions and might be therapeutically targetable. Here we present data on the role of three plasma membrane-localized palmitoyltransferases expressed in pancreatic beta cells in the regulation of GLP-1R responses downstream of exendin-4 stimulation. To examine this, we have engineered murine MIN6B1 beta cell lines using CRISPR/Cas9 to delete the expression of the plasma membrane palmitoyltransferases ZDHHC5, 20 and 21. We observe a reduction in exendin-4-induced cAMP production and incretin-stimulated insulin secretion in ZDHHC20 and 21 knockout compared to control cells, while ZDHHC5 deletion leads to increased cAMP and insulin responses downstream of GLP-1R activation. Experiments are underway to analyze the possible effects of knocking out these three palmitoyltransferases on the palmitoylation of the GLP-1R or related downstream effectors such as beta arrestins or G proteins, as well as on the dynamic behavior of the receptor in the lipid bilayer, in order to explain their identified impact on beta cell function.

DOI: 10.1530/endoabs.65.P206

P207

Visfatin and resistin as predictors of poor pain outcome in total hip and knee joint replacement in patients with osteoarthritis

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With an aging population the number of total joint replacements performed due to end-stage osteoarthritis is increasing. Critically, a significant proportion of patients report dissatisfaction following surgery, with around 10% of hip and 20% of knee OA patients developing chronic postoperative pain. Obesity is a well-known risk factor for the development of OA. Pre-surgical obesity has been previously associated with worse clinical outcomes following arthroplasty. Therefore, the aim of this study was to identify factors secreted by adipose tissue that might contribute to poor outcome of arthroplasty. In total, 160 OA patients who were scheduled to undergo arthroplasty were recruited. Pre-operatively, anthropometric data were recorded. Patients completed EQ-5D health status and Oxford Knee Score (OKS) questionnaires pre-operatively and at 7 month post-operatively. Peri-operatively, synovial fluids (SF) were aspirated from the joint and the concentration of 24 adipose-secreted cytokines (adipokines) quantified by Luminex assay. Comparing pre-operative and post-operative EQ-5D index, 87% ($n=139$) of patients had positive response outcomes and were classified as 'responders'. The remaining 13% ($n=21$) of patients, who either had a negative outcome or no improvement, were classified as 'non-responders'. Including all patients, there was a significant correlation between ΔEQ-5D scale with BMI (Spearman $r=-0.29$, $P=0.03$) and with the degree of obesity (Spearman $r=-0.40$, $P=0.045$). Analysis of pre-operative SF revealed that non-responders had significantly lower median concentrations of resistin [1642 ng/ml (943.8–3516) vs. 3080 ng/ml (2235–6561); $P<0.048$], compared to responders. In addition, SF visfatin median concentrations were lower in non-responders, (0 ng/ml(0–0) vs. 3746 ng/ml (0–45 947); $P=0.025$], compared to responders. Poor patient outcomes in OA patients following knee and hip total joint replacement surgery are associated with differences in the pre-operative SF concentration of visfatin and resistin and with greater adiposity. Further analysis of both baseline and post-operative SF adipokines profiling together with patient's anthropometrics data could provide the basis for a predictive tool to guide clinicians.

DOI: 10.1530/endoabs.65.P207

P208

Assessment of cardiovascular disease risk in subjects with pre-diabetes

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Introduction

Prediabetes carries a risk of diabetes and cardiovascular disease (CVD). Assessment of CVD risk in prediabetes is not as routine, as is assessment of diabetes risk. However, it is not less important. This can be done through conventional SCORE charts and through coronary artery calcium (CAC) score. CAC is examined through multislice CT. Calcifications indicate late-stage subclinical coronary atherosclerosis. The AIM of our study was to assess traditional CVD risk through score charts and CAC in subjects with prediabetes (preDM) and to evaluate whether any correlation exists between the two.

Methods

After diagnosing preDM with oral glucose tolerance test and HbA1c, ECG was performed and subjects were evaluated for CVD risk through Score charts. Thereafter, all subjects were appointed for multislice CT to obtain the CAC.

Results

80 subjects with preDM were screened for CVD. CAC score of 0 was present in 35 subjects. Minimal calcifications with a CAC score of 1–10 AU were present in 10 subjects with pre DM. Moderate calcification of 11–100 AU were present in 18 subjects. 12 subjects had significant calcifications with 101–400 AU. Five subjects had a CAC score >400 AU. Score risk below 2% was present in 20 subjects. Score risk of 3–4% was present in 10, 5–9% risk was present in 16 and a score risk of 10–14% was present in 8 subjects. Twenty six subjects with PreDM has a score risk of 15% and more. No significant correlation was found between Score charts and CAC. However, a trend of finding more calcifications in those with a 10% and above Score risk was noted.

Conclusion

An approach to risk assessment that combines the traditional Score charts with a more personalized atherosclerosis-imaging model may be appropriate for high risk subjects with pre diabetes.

DOI: 10.1530/endoabs.65.P208

P209

Maternal diet-induced cholestasis programmes murine offspring metabolic impairment on feeding a Western diet, with altered intestinal metabolites and microbiota in the female offspring

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Background
The 16-year-old children of mothers with intrahepatic cholestasis of pregnancy demonstrate increased adiposity, dyslipidaemia, and males have raised fasting insulin. Similarly, the offspring of cholestatic pregnant mice have impaired glucose tolerance and dyslipidaemia when challenged with a Western diet. Female offspring have a more marked phenotype than males. Bile influences microbial growth, thus intestinal bile acid exposure in pregnancy may contribute to metabolic impairments observed. We hypothesise that the offspring of cholestatic pregnancies develop an abnormal gut bacterial and metabolite composition, contributing to the offspring's phenotype.
Methods
C57BL/6 female mice were fed normal chow or 0.5% cholic acid-supplemented diets and mated. Their offspring were fed normal chow or Western diets. Ultra-performance liquid chromatography – mass spectrometry was used to assess the caecal metabonome. Metataxonomics was performed to determine the caecal microbiota. Results were compared using OPLS-DA, PCA, NMDS, and T-tests with Benjamini–Hochberg correction for multiple measures.
Results
The offspring microbiota was significantly affected by maternal and neonatal diet, with a sex difference in bacterial composition revealed in the pups of mothers fed cholic acid, when fed a Western diet. The female offspring of cholic acid-fed mothers had a higher abundance of *Alistipes*, a bile acid-resistant member of the *Bacteroidetes* phylum, than males. This group had lower caecal bile acids ($P=0.036$) (particularly deoxycholic acid, cholic acid and ω-muricholic acid) than offspring of normal chow-fed mothers when challenged with a Western diet.
Conclusions
Maternal cholic acid feeding results in increases in bile-resistant bacteria in the caecum of female offspring. A gender difference in the microbiome and bile acid content of the caecum is revealed by a Western diet. Together, these findings demonstrate how the establishment of the offspring gut microbiome, and associated metabonome, is influenced by an altered maternal environment, contributing to increased long-term risk of metabolic impairment.

DOI: 10.1530/endoabs.65.P209

P210

All cause and cardiovascular mortality in adults with schizophrenia and diabetes – a retrospective matched study

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Introduction
Increased prevalence of diabetes is found in major psychosis, and poorer outcomes occur when both diagnoses co-exist. The aim of this study was to describe the association between total and cardiovascular mortality in people with both schizophrenia and diabetes, compared to diabetes alone.
Materials and methods
Data was linked from the Glasgow Psychosis Clinical Information System (PsyCIS), the Scottish national diabetes database (SCI-Diabetes), and national death certification data. The Scottish Index of Multiple Deprivation (SIMD) 2016 quintile for each patient was obtained using their residential postcode. Schizophrenia was defined using International Classification of Diseases, Tenth Revision (ICD-10) codes F20 (schizophrenia) and F25 (schizoaffective disorder). Cases (schizophrenia and diabetes) were matched by age (+/− 1 year), gender and deprivation quintile to those with diabetes but not present on the PsyCIS database (controls). Follow up 01/01/2002 to 16/8/2018. Standard descriptive statistics and survival analysis undertaken, adjusted for age.
Results
702 individuals in each cohort. 64% male. Mean age at index 41 years. 414/702 (59%) were in the most deprived quintile. Mean body mass index (BMI) at diagnosis, or in preceding 12 months, available for 450/702 controls, and 446/702 cases. Mean (s.d.) BMI 33.53 (6.75) for controls and 33.23 (6.58) for cases, no statistical difference. At study end 63/702 controls were dead, 133/702 cases. Hazard ratio 2.34 (95% CI 1.76 to 3.21, P value <0.001). Cardiovascular diagnosis was noted in death certification in 34/702 controls and 51/702 cases. Hazard ratio 1.716 (95% CI 1.110 to 2.653, P value <0.05).
Conclusion
This study demonstrates significant excess all cause mortality and cardiovascular death over and above that expected with diabetes, despite our cohorts being matched for deprivation. Lower thresholds for starting cardiovascular prevention medications may be indicated in individuals with diabetes and schizophrenia. Using routinely collected data has limitations, and missing data can be substantial.

DOI: 10.1530/endoabs.65.P210

P211

Glycated haemoglobin and obstetric outcomes among patients with gestational diabetes mellitus: a single center study

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Introduction
Despite the established role of HbA1c in assessing chronic glycaemia, its role the management of gestational diabetes mellitus (GDM) is still unclear. We aimed to determine the association between HbA1c and obstetric outcomes among our patients with GDM.
Methods
We reviewed the antenatal records of 512 singleton pregnant women followed up in our center. Among the 180 patients that did a 75 g Oral Glucose Tolerance Test OGTT, 64 met the IADPSG criteria for GDM. Sociodemographic, clinical and laboratory parameters were extracted for the patients with GDM. The associations between HbA1c and variables including insulin treatment, birth weight, maternal and neonatal complications were analysed.
Results
The mean age of the subjects with GDM was 33.2 $\pm$ 4.7 years and 12% had a previous history of GDM. In the OGTT profile the 0 min was the most commonly abnormal OGTT parameter using the IADPSG – which was abnormal in 72% of the patients, compared to the 60 and 120 min which was abnormal in 44% and 42% respectively. Among the subjects, 20% required insulin therapy, 72% required a Caesarean section (CS) while 17% had birth weight > 4.0 kg. Maternal and neonatal complications occurred in 42% and 34% of the patients respectively. HbA1c correlated with the OGTT parameters, (r = 0.76, 0.54 and 0.55 for 0, 60- and 120-min glucose respectively; $P<$ 0.05). The mean HBA1c among the patients that required insulin was higher than those who did not (8.7 $\pm$ 1.6% vs. 6.3 $\pm$ 1.3%; P < 0.05). There was no association between HbA1c values and birth weight, need for CS, maternal or neonatal complications.
Conclusion
Although Hba1c is useful in predicting the need for insulin therapy, it is not significantly associated with birth weight, maternal or neonatal outcomes among patients treated for GDM.

DOI: 10.1530/endoabs.65.P211

P212

An audit of SGLT2-inhibitors in the management of type 2 diabetes in Sligo University Hospital Ireland: metabolic and haemodynamic outcomes

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Introduction
Sodium-Glucose Co-Transporter-2 (SGLT2) inhibitors are the latest class of anti-hyperglycaemic agents which reduce blood glucose by increasing urinary glucose excretion.

Aims

1) To assess the metabolic and haemodynamic changes associated with SGLT-2 inhibitors in patients attending Sligo University Hospital (SUH) Ireland.
2) To enhance prescriber awareness across disciplines regarding the metabolic and haemodynamic benefits in addition to improving cardio-renal outcomes as demonstrated in the EMPAREG, CANVAS & DECLARE meta-analysis

Methodology

After screening for eligibility, we selected 98 patients prescribed SGLT2-Inhibitors between January 2014 to December 2018. We excluded those with incomplete data and whose medications were stopped during the initial 6-month period. Retrospective data was collected from Medical Charts, NIMIS®, IPMS® and ProWellness IT Diabetes Database®. Data was collected at Baseline and at 6 months after the start of SGLT-2i for body weight, blood pressure, HbA1c and lipid profile.

Mean HbA1c was 8.89(1.44) % at baseline which dropped significantly to 8.04(1.22) % at 6 months. A similar highly significant change was observed when comparing weights at baseline and 6 months: 95.49(20.5) kg to 93.29(19.6)kg. Blood pressure changes were remarkable but there was only a modest improvement of HDL with no significant changes in Total Cholesterol, LDL and Triglycerides.

Results

Baseline Characteristics ($n=98$)

Age (Years)	62.13 ± (12.29)
DM Duration (Years)	1–29
Median Treatment (Years)	2
Sex (Male/Female)	61/37

Changes in The Examined Variables After 6 Months Of Starting SGLT2-Inhibitors

	Pre-Treatment	6 Months	*P*
HbA1c (%)	8.80	8.04	<0.0001
Systolic Blood Pressure (mmHg)	143.75	135.41	<0.0001
Diastolic Blood Pressure (mmHg)	80.60	77.96	<0.0001
Weight (kg)	95.49	93.29	<0.0001
HDL-C (mmol/l)	1.154	1.095	0.004

Conclusion

The use of SGLT-2 Inhibitors in SUH was associated with significant metabolic and haemodynamic improvements which were better than expected when compared with those documented in large volume trials

DOI: 10.1530/endoabs.65.P212

P213

Determinants for developing foot ulcer among persons with diabetes mellitus attending outpatient clinic in a tertiary hospital in Nigeria

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Introduction

Diabetic foot ulcer (DFU) is a chronic complication not desired in individuals with Diabetes Mellitus (DM). It reduces the productivity and economic power of affected persons. Identifying risk factors leading to development of DFU is of paramount importance in preventing its occurrence.

Objective

To identify risk factors for DFU in diabetes outpatient clinic of Lagos University Teaching Hospital.

Method

This was a cross-sectional study in which 296 consenting individuals with DM were enrolled. Interviewer-administered questionnaire utilized included history of previous ulcers, burning sensation, numbness, intermittent claudication, pin and needle sensation and visual impairment. Patient were assessed clinically with emphasis on foot examination. Anthropometric and biochemical measurements were also obtained. Data was analysed using SPSS version 25. P value ≤ 0.05 was considered significant.

Result

The mean age of participants was 60.58 ± 11.3 years of which females were 61.8%. twenty-three (7.8%) had past history of DFU. Risk factors identified for development of DFU included visual impairment (63.2%), skin dryness (52%), inappropriate footwear (51.7%) pin and needle sensation (50.3%), numbness (39.4%), hair loss (32.8%), cracks (29.4%), burning sensation (24%), lower limb oedema (17.2%), dilated veins (6.4%), wasting of small muscles of the foot (5.7%), DVT (2.4%). Identified predictors for development of DFU includes duration of DM ($P<0.014$), history of overweight/obesity ($P<0.035$), inappropriate foot wear ($P<0.05$) and cracks ($P<0.003$) while glycaemic control was not statistically significant.

Discussion

DFU among participants is less than 10% however to prevent increasing incidence of this complication identified risk factors need to be curtailed. Leading predictors for development of DFU includes duration of diabetes >10 years, presence of cracks and inappropriate footwear.

Conclusion

Regular screening for DFU risk factors in our day to day practice is essential and inappropriate foot wear should be discouraged especially in patients with prolonged history of DM.

DOI: 10.1530/endoabs.65.P213

P214

Hypoglycaemia screen (hypopak) quality improvement audit

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In Northern Ireland hypopaks (contains samples for glucose, lactate, hydroxybutyrate, insulin, growth hormone (GH), cortisol, amino acids, organic acids and acylcarnitines) are used to investigate hypoglycaemia in children. We aimed to assess the appropriateness of hypopak requests, to determine their usefulness in diagnosing endocrine and metabolic conditions and to determine if GH is helpful. Data for hypopaks received between 01 April 17 and 31 March 18 was analysed. Hypopaks with unrecorded glucose or glucose ≥3 mmol/l were excluded. In total 223 hypopaks were received from 210 patients: 51% (113 hypopaks) were from girls; 67% samples came from children <3 years; only 36% (80 hypopaks) had complete results. Of the 113 samples with laboratory glucose <3 mmol/l, 21% had glucose <2 mmol/l with 2.7% having glucose <1 mmol/l. There were 25 samples with detectable insulin when glucose was <3 mmol/l (3 samples were from 1 patient thus 23 patients total). Three samples were taken post dextrose. Eight patients had samples sent during the neonatal period. Seven had no follow-up, the rest attend relevant clinic. Of the 113 samples with lab glucose <3 mmol/l, 82% ($n=92$) had GH <6.7 ng/ml. Only 20 (18%) showed appropriately raised GH. 5/6 patients with GH <1 ng/ml had congenital abnormalities, the other had gastroenteritis. There were 24 hypopaks for children with glucose <3 mmol/l and cortisol <450 nmol/l. One child had 2 hypopaks thus there were 23 children in total. Of these 14 never had a short synacthen test (SST) performed. Three had inadequate SST, 3 had adequate SST response. On later samples the other 3 children showed adequate cortisol on hypoglycaemia. This audit has shown that only 51% of hypopaks received had glucose <3 mmol/l, 74% had incomplete results and no cases of short stature were detected using GH in hypopaks. We propose to develop guidelines for appropriate requesting of hypopaks and result interpretation.

DOI: 10.1530/endoabs.65.P214

P215

Bariatric surgery outcomes amongst older obese patients: data from an Emirati cohort

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Background
Obesity is highly prevalent in the Middle East. Treatment is a challenge and with an aging population, therapy in the elderly poses new problems. Published data on efficacy of bariatric surgery in the older age groups are scant.
Aims
The objective of this study was to assess the outcomes of bariatric surgery (BS) in the elderly ($\geq$65 years) in the UAE population.
Methods
ICLDC patient database was accessed to identify all patients with a history of BS after the age of 65. Anthropometric measurements, medications, diabetes status and HbA1c were extracted. Data are presented as median (interquartile range).
Results
22 Emirati patients [12 females, age 66.9 (66.2–67.8) years, BMI 43.6 (40.4–46.8) kg/m^2, 19 with type 2 diabetes with a duration of 6.75 (2.94–13.21) years] who had sleeve gastrectomy (LSG, $n=15$) or Roux-en-Y gastric bypass (RYGB, $n=7$) were identified. At two years after surgery there was significant weight loss of 23.9 (15.4–28.5) % ($P< 0.001$) with a BMI reduction of 10.8 (6.7–13.9) kg/m^2. Total weight loss was comparable between LSG and RYGB ($P= 0.238$). Median reduction in HbA1c was 0.9 (0.6–1.3) % at two years after surgery. Two patients who had impaired fasting glucose had normal glucose tolerance within six months after surgery. There was a significant dose reduction amongst insulin treated patients [$n=11$; 120 (70–165) vs. 25 (20–35) units, $P= 0.08$)] with 4/11 patients completely off insulin. Duration of diabetes had no effect on weight loss or HbA1c reduction post BS. Reported adverse effects included iron and vitamin D deficiency ($n=14$).
Conclusions
Our data suggest that successful weight loss and better glycaemic control can be achieved in the elderly and that age alone should not be considered a contraindication to bariatric surgery.

DOI: 10.1530/endoabs.65.P215

P216

Risk of sleep apnoea among Emirati patients with type 2 diabetes

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Background
Type 2 diabetes (T2D) and obesity have been linked with sleeping disorders in general and obstructive sleep apnoea (OSA) in particular; both are highly prevalent amongst Emirati patients. However, little information is available in this population regarding the prevalence and symptomatology of OSA, its relationships with T2D and obesity, and its impact on health outcomes.
Objectives
This study aims to investigate the risk of OSA based on the STOP-BANG questionnaire, a previously-validated screening tool for OSA, among Emirati patients seen at Imperial College London Diabetes Centre (ICLDC).
Methods
Individuals attending ICLDC for indications other than diabetes were recruited by convenience sampling and asked to complete the Arabic-translated STOP-BANG questionnaire. Other relevant information were retrieved from the centre's electronic database with the consent of participants. Data presented as mean $\pm$ S.D.
Results
700 Emirati individuals (51.9% female, age 43.4 $\pm$ 12.3 years, BMI 30.5 $\pm$ 6.1 kg/m^2) took part in the study. 46% of those recruited had an established diagnosis of T2D. STOP-BANG screening results showed high risk of OSA in 19.6%, intermediate risk in 34.7% and low risk in 45.7% of participants. High scores were more prevalent amongst patients with T2D compared to normoglycaemic individuals (31.5% v 5.5%). In male participants, snoring was the most commonly reported marker (73.2%), while in female participants, tiredness was more common (53.4%).
Discussion
Based on the STOP-BANG criteria, more than half of the studied population are at high or intermediate risk for OSA with high prevalence amongst patients with T2D. Our findings also indicate the need for proactive screening in these individuals.

DOI: 10.1530/endoabs.65.P216

P217

A novel method for analysis of 11 oestrogens using high-throughput liquid chromatography tandem mass spectrometry

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Oestrogen quantification in serum is challenging as concentrations are low, especially in men and post-menopausal women. Additionally, oestrogens do not ionise readily and structure similarities can lead to cross-reactivity and reduced specificity, especially with immunoassay. Full characterisation of oestrogen metabolism and its role in disease progression has therefore not been fully investigated. We aimed to develop and validate a liquid chromatography mass spectrometry method which separates 11 oestrogens and demonstrate its utility for *in-vitro* experiments and biological samples. Mass spectrometry parameters were optimised for each oestrogen on a Waters Acquity UPLC chromatography system coupled to a Waters Xevo TQ-XS mass spectrometer and electrospray ionisation source. Oestrogens were subsequently combined and eight columns from Waters and Phenomenex were screened to optimise chromatographic separation using a methanol/water (both with 0.1% formic acid) elution system. The column which provided the most favourable chromatographic parameters, Phenomenex Kinetex F5 2.6 µm 50$\times$2.1 mm, was further optimised via gradient and investigation into mobile phase additives to produce an 8 min method with baseline resolution of all analytes. LOQ was less than 0.5 ng/ml for oestrone, oestradiol, 2-methoxyoestradiol and 16-hydroxyoestrone, 1 ng/ml for 11b-OHoestradiol, and 2-methoxyoestrone, and 5 ng/ml for oestriol and the 2 and 4 hydroxylated oestrogens. Accuracy (%bias) and precision (%CV) were assessed at 3 levels of concentration (low 2 ng/ml, medium 20 ng/ml and high 200 ng/ml). Accuracy ranged from 1 to 19, -4 to 16, and -8 to 10% (low, medium and high), precision ranged from 8 to 19, 3 to 17 and 3 to 9% (low, medium and high) excluding the 2 and 4 hydroxylated oestrogens below LOQ. Further experiments are under-way to improve sensitivity and extraction efficiency. This novel method separated 11 structurally similar oestrogens in 8 min and can now be applied to oestrogen analysis *in-vitro* and in biological samples.

DOI: 10.1530/endoabs.65.P217

P218

Inhibition of nicotinamide phosphoribosyltransferase (NAMPT) prevents cytokine-mediated beta cell dysfunction

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Intracellular nicotinamide phosphoribosyltransferase (NAMPT) is the rate-limiting enzyme in the NAD salvage pathway. Abnormally elevated NAMPT can promote autoimmune and inflammatory processes. Many of these processes are key to type 1 diabetes (T1D) pathogenesis. Whilst NAMPT has been examined in other inflammatory diseases, the role of NAMPT in T1D remains unclear. To investigate the role of NAMPT in T1D, we used small molecule NAMPT modulators to determine the role of abnormally elevated NAMPT levels and activity in cytokine-mediated beta-cell death and dysfunction in mouse and human islets. Islets were isolated from Cd1 mice and incubated for 24 h with either NAMPT inhibitor (10–20 nM FK866 or 200–400 nM C17) or activator (5–10 µM P7C3) +/− proinflammatory cytokine cocktail (1 ng/ml). Islet function and survival were assessed via static glucose-stimulated insulin secretion (GSIS) assays, Caspase 3/7-glo bio-luminescence assay, and qPCR analysis. NAMPT inhibition protected islets against cytokine-induced apoptosis; cytokine-mediated caspase 3/7 activity was significantly reduced by ~55% ($P<0.01$; C17)

and ~48% ($P<0.001$; FK866), compared with cytokine treatment alone. Co-incubation with 5 μM P7C3 exerted no significant changes in apoptosis compared to cytokine treatment alone ($n=3$). The pro-survival effects of NAMPT inhibition were not due to changes at gene expression level in either *IL-1B* or *TNFA,* nor in markers of intrinsic apoptosis (*BAX*, *BAD* & *NOXA*) since mRNA levels of these genes were unchanged between islets co-incubated with C17 and cytokines and islets incubated with cytokines alone ($n=3$). In addition, NAMPT inhibition with C17 or FK866 protected islets against pro-inflammatory cytokine-mediated reductions in GSIS (both $P<0.0001$). Surprisingly, P7C3 also exerted mild protective effects against cytokine-mediated reductions in GSIS (NS; $n=2$). NAMPT inhibition reversed cytokine-mediated beta-cell apoptosis and dysfunction. This suggests that NAMPT may play a pathophysiological role in mediating inflammation-induced beta-cell damage and thus, may be a therapeutic target.

DOI: 10.1530/endoabs.65.P218

P219

Predicting mortality in both diabetes and open-source clinical datasets from free text entries using machine learning (natural language processing)

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Objective
We aimed to test the utility of semantic analysis to predict all-cause mortality from free-text entries from both a national diabetes database, and an open source clinical dataset (MIMIC-III). We analysed text entries alone, in order to fully understand the potential of language analysis to predict outcome.
Method
Diabetes dataset: An analysis period of 3 years was defined during which clinical text data were extracted. Mortality status at 1 year was identified. Data was preprocessed and divided randomly into training/validation and test sets 0.8:0.2. The training/validation set was further randomly divided 0.8:0.2. Dimensionality reduction was performed using embedding, and a combined convolutional and recurrent (LSTM) neural network was trained on the training subset for 20 epochs. Class imbalance was managed by applying class weights. A prediction of outcome was made on the withheld test set using the trained model, and area under receiver operator characteristic curve (AUROC) was calculated. MIMIC-III dataset. A similar methodology was applied, with some further development of sophistication of neural network architecture.
Result
Diabetes dataset: 53 954 individuals with data were identified. 2292 deaths were recorded at 1-year post analysis. AUROC of model predictions when applied to withheld testset was 0.62.
MIMIC-III
11 518 individuals identified, with 2045 deaths at 1 year. AUROC applied to withheld testset 0.86.
Conclusion
By learning from clinician's summaries, NLP has the potential to leverage the clinical understanding of multiple clinicians and integrate information from multiple data sources. These models may be trained on outcomes such as mortality, aiding risk stratification, or on outcomes such as response particular therapeutic agents, aiding clinical decision making.

DOI: 10.1530/endoabs.65.P219

P220

GLP-1/Glucagon dual agonist affects amino acid metabolism

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Background
GLP-1/glucagon dual agonists are being developed as treatments for obesity due to their combined effect of reducing food intake while increase energy expenditure. Though the effect of the dual agonist on carbohydrate and lipid metabolism is well studied, little is known about the effects on protein metabolism. This study aimed to examine the acute and chronic effects of the GLP-1/glucagon dual agonist on amino acid metabolism.
Methods
The long-acting GLP-1/glucagon dual agonist analogue, OX-SR, or a vehicle control, was administered to male Wistar rats either as a single dose ($n=8$), or as a daily dose for 22 days as part of a pair-feeding paradigm ($n=9$). Plasma, liver and muscle samples were taken 4 h after the single injection, and 24 h after the final injection in the chronic study. Plasma amino acids were measured and qPCR of hepatic urea cycle enzymes Argininosuccinate Synthetase (*Ass*) and Carbamoyl Phosphate Synthetase (*Cps*) as well as muscle-specific E3 ubiquitin ligase enzymes Atrogin-1 and MuRF-1 were undertaken. Urine volume and urea concentration measured over the last 16 h of the chronic study.
Results
Both acutely and chronically, OX-SR significantly reduced plasma amino acids independently of food intake. There was also a significant increase in the hepatic urea cycle enzymes at both time points. Acutely, OX-SR did not effect on muscle-specific ligases; chronically there was an elevation in both Atrogin-1 and MuRF-1. In the chronic study, there was a non-significant increase urine output and total urinary urea excretion.
Conclusions
This data suggests that the GLP-1/glucagon dual agonist, OX-SR enhances hepatic uptake of amino acids with subsequent deamination to urea, *in vivo*. Chronically, there is also degradation of muscle proteins to sustain these changes. Further investigation in to the effect of these analogues in humans is required.

DOI: 10.1530/endoabs.65.P220

P221

A digital lifestyle programme to support outpatient treatment of type 2 diabetes: a randomised controlled trial

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Background
Lifestyle is important in the treatment of type 2 diabetes. The aim of this study was to investigate whether a lifestyle programme through a smartphone application (digital therapeutic) could affect treatment outcomes at an endocrinology outpatient clinic.
Methods
In this randomised controlled study, patients were consecutively invited to participate. Participants were randomly assigned to an intervention group or a control group. In addition to standard care, intervention group participants used a smartphone application that gave access to the lifestyle programme, through which they received personalized recommendations and clinical-guideline-compliant education about healthy lifestyle. Both groups visited the clinic every other month for six months for follow-up measurements, including body weight and blood tests for glycated haemoglobin (HbA1c) and blood lipids. Furthermore, all participants filled in questionnaires about distress related to diabetes, health-related quality of life, depression and anxiety. Statistical methods included parametric and nonparametric tests for comparisons both within and between groups.
Results
A total of 37 patients (23 women) were included, whereof 30 finished, 15 in each group (19% dropout), average age 52.7 $\pm$ 10.6 (25–70) years. No significant differences emerged between the groups, but within the intervention group there was a significant decrease in HbA1c, from 61 $\pm$21.4 to 52.7 $\pm$15.2 mmol/mol. Furthermore, the intervention group saw a decrease in disease-specific distress (Problem Areas In Diabetes Scale from 19.5 $\pm$16.5 to 11.7 $\pm$13.4) and anxiety symptoms (from 5.4 $\pm$4.0 to 4.1 $\pm$3.8). No significant changes occurred in the control group over the six-month research period. Usage of the app in the intervention group was most frequent during the first months and differed interpersonally.
Conclusions
Our results indicate that a digital lifestyle programme could enhance outpatient treatment outcomes in type 2 diabetes, in terms of both glycaemic control and psychological health.

DOI: 10.1530/endoabs.65.P221

P222

FSH levels are adversely associated with markers of regional adiposity in postmenopausal women

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Background
A growing body of evidence reports implications of a direct extra-gonadal effect of follicle stimulating hormone (FSH), involving the development of obesity. The aim of this study was to evaluate the associations between traditional and local obesity indices and FSH concentrations in women after menopause.
Methods
We evaluated a total of 420 postmenopausal women in a cross-sectional design (age 55.6±6.5 years, BMI were 25.8±4.0 kg/m^2, 8.01±6.7 years since menopause) with low insulin resistance (homeostasis model assessment of insulin resistance, HOMA-IR<5) We recorded anthropometric parameters and evaluated the body mass index (BMI). Indices of regional adiposity were sonographically assessed and included preperitoneal fat and subcutaneous fat). Fasting blood samples were obtained for biochemical and hormonal evaluation.
Results
Values of BMI and waist circumference exhibited an inverse association with increasing quartiles of FSH (BMI, FSH Q1 vs. Q2 vs. Q3 vs. Q4: 27.6±5.2 vs. 26±4.8 vs. 25.8±7.1 vs. 23.9±2.9; Waist, FSH Q1 vs. Q2 vs. Q3 vs. Q4: 93.2±2.4 vs. 87.6±4.4 vs. 85.4±1.8 vs. 80.89±2.8; ANOVA *P*-value for linear trend <0.001, both cases). Similarly, values of subcutaneous and preperitoneal fat exhibited a linear decrease with increasing quartiles of FSH (ANOVA *P*-value for linear trend <0.001). Multivariable stepwise linear regression analysis showed that preperitoneal fat measures were inversely associated with FSH levels (*b* coefficient= −0.130, *P* value=0.029), independently of traditional cardiovascular risk factors and circulating estrogen. The association between subcutaneous fat measures and FSH was lost following adjustment for circulating estrogen, implying a possible mediation effect of estrogen on this association.
Conclusions
Serum levels of FSH are inversely associated with markers of regional and total adiposity in postmenopausal women. The exact mechanism of this interaction remains to be elucidated in future studies.

DOI: 10.1530/endoabs.65.P222

P223

Untreated pre-operative mental illness is associated with poorer bariatric surgery outcomes

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Background
Approximately 20% of bariatric surgery candidates are excluded for reasons of mental health. All bariatric patients undergo a pre-operative assessment of suitability, including a mental health assessment. There are no NICE guidelines as to what level of mental illness is considered an exclusion; it is generally regarded that 'unstable mental health' is a contraindication to surgery. The main reason is concern regarding adherence to essential lifestyle changes post-surgery.
Methods
We retrospectively analysed data from 100 consecutive patients who had bariatric surgery at King's College Hospital in 2017. Patients were divided into groups based on their pre-operative history of mental illness. We also analysed whether they had been actively treated for mental health problems. The primary outcome looked at was percentage weight loss at 12 months.
Results
The main finding was that patients with a single mental illness diagnosis (depression or anxiety) lost significantly less weight, compared to those with no history of mental illness (23.4% vs. 29.2%; $P=0.005$). Conversely, those with multiple or more complex mental health diagnoses, such as bipolar and/or schizophrenia, achieved good weight loss comparable to the group without mental health diagnoses. Further analysis revealed that the groups with untreated mental health diagnoses appeared to lose less weight following bariatric surgery, compared to patients being actively treated.
Conclusion
The study indicates that not all mental health diagnoses are associated with a worse outcome following bariatric surgery. It is untreated pre-operative mental illness who have the worst weight loss outcomes. Patients with treated mental health diagnoses, have similar outcomes to those without a mental health diagnosis. These results suggest more attention needs to be given to whether a mental health condition is being actively treated. The results also potentially indicate a need to revise guidelines on suitability for bariatric surgery, in relation to mental health.

DOI: 10.1530/endoabs.65.P223

P224

Regulation and role of MiR-125b in β-cells

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MicroRNAs (miRNAs) are small non-coding RNAs that repress protein production post-transcriptionally. MiRNAs play crucial roles in metabolism, endocrine cells development and in processes altered in T2D, such as insulin secretion. MiR-125b controls proliferation, apoptosis and differentiation of various cell types, although its role in β-cells remains unclear. Recent studies show an association between high levels of circulating miR-125b and hyperglycaemia (HbA1c) in prediabetes, T1D and T2D, suggesting this miRNA as a biomarker/contributor to the disease. I aim to determine whether glucose regulates miR-125b expression in β-cells and to understand its function by identifying its gene targets. We found that miR-125b expression is regulated by glucose in both mouse and human islets *via* AMP-activated protein kinase (AMPK), an important regulator of glucose homeostasis and target for anti-diabetic drugs. A combined analysis of both RNA-Seq and RNA-Immuno-precipitation of the miRNA-induced silencing complex (RIP-Seq) in β-cells overexpressing miR-125b identified dozens of novel miR-125b targets such as *M6pr* and *Mtfp1*, involved in enzyme sorting within secretory granules and mitochondrial fission and revealed a role for miR-125b in respiration and cytokine receptor interactions. Thus, miR-125b arises as an important regulator of β-cell function with a potential role in the deleterious effects of hyperglycaemia on β-cells.

DOI: 10.1530/endoabs.65.P224

P225

Refeeding syndrome induced hypertriglyceridemia

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Introduction
Hypertriglyceridemia is an established complication associated with some parenterally fed patients. In healthy individual, lipid particles are hydrolyzed to release fatty acids via the action of lipoprotien lipase (LPL) which used eventually for energy or stored in adipose tissue. In stressed patient, the activity of LPL is decreased. We present a 16-year-old girl, who is a known case of acute myeloid leukemia on chemotherapy, was admitted to the hospital with sepsis for which she started on antibiotics.Was unable to tolerate orally. She was started on TPN after

dietitian assessment. TPN was started as per protocol which contains amino acids, dextrose and heparin without lipid emulsion. Two days later, triglyceride level started to increase gradually. Her blood glucose level was normal. Her liver enzymes was normal. TPN was stopped when TG reached 6.39 mmol/l, dropped next day to 4.25, then 2.22 mmol/l, till it went back to her baseline. The patient did not receive steroid with the TPN. Heparin dose was less than the expected dose to cause hyperglyceridemia. Labs showed a decrease in levels of phosphorus, magnesium, and potassium after initiation of the TPN, which indicating that the patient was having refeeding syndrome. During starvation, the basal metabolic rate and insulin levels will fall while glucagon levels rise. glycogen stores are utilized to release glucose, but after 2–3 days gluconeogenesis from amino acids has taken over, accompanied by lipolysis of fat stores. When feeding is recommenced, there is a surge in insulin and fall in glucagon accompanied by a marked rise in metabolic rate. Hydrolysis of triglycerides is inhibited, glucose uptake by adipocytes is stimulated, glycogenesis recommences, and amino acid synthesis promoted. To our knowledge, this is the first case report addressing the direct effect of refeeding syndrome causing hypertriglyceridemia.

DOI: 10.1530/endoabs.65.P225

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Are PCSK9 inhibitors delivering as promised?

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Background and aims
Statins has long been used as first line treatment option for hypercholesterolemia however; half of population doesn't achieve target LDL reduction. Proprotein convertase subtilisin kexin 9 inhibitors (PCSK9i) are a promising addition to anti-dyslipidemic armamentarium. Aim of this study is to find out the efficacy of PCSK9 inhibitors in a district general hospital of Northwest of England.
Method
We identified all the patient who have been prescribed PCSK9 inhibitors in last 3 years from home care pharmacy record and had at least 2 lipid profile done at baseline before starting PCSK9 inhibitors and latest at least 6–12 months later.
Results
Our study included 11 patients; all of them were on Evolocumab 120 mg every 2 weeks. 54.5% ($n=6$) had definite FH, 27.2% ($n=3$) had possible FH and 18.1% ($n=2$) had polygenic hypercholesterolemia. 36.3% ($n=4$) of patients were statin intolerant. Amongst statin intolerant group of 4 patients, 1 patient had serious side-effects with PCSK9i needing withdrawal of treatment. Amongst the patients who tolerated PCSK9i, median baseline LDL-C was 5.9 mmol/l and median LDL-C 6–12 months post PCSK9i treatment was 1.65 mmol/l with mean reduction of 58%. Side effects were reported in 18.1% ($n=2$) patients, 1 of them were previously intolerant to statins and treatment has to be discontinued in that patient. Mean reduction in LDL-C in patients intolerant to statins who tolerated PCSK9i was 56%, while mean reduction in LDL-C was 59% in patients who tolerated both statins and PCSK9i.
Conclusion
Our observation shows that mean LDL-C reduction with PCSK9 inhibitors in routine clinical practice is comparable to FOURIER, ODYSSEY ALTERNATIVE and GUASS-3 trial.

DOI: 10.1530/endoabs.65.P226

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Bariatric surgery outcomes in super obese Emirati patients

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Background
Efficacy of bariatric surgery (BS) in obesity management is well-established. The super-obese (BMI >50 kg/m^2) as a subgroup may have specific phenotypic and genotypic characteristics. Prevalence of complications and risks of interventions may also be different in this group.
Aims
We have investigated BS outcomes and compared effects of different operations among the superobese in an Emirati population.
Methods
The ICLDC electronic database was accessed to identify super obese patients with previous bariatric surgery. Relevant pre and post surgical data including age at surgery and BMI were extracted from the database and from individual patient records. For patients who had undergone BS more than once, the last type of BS performed was considered in the analysis. Total weight loss following surgery was calculated from the lowest weight reported post BS. Data presented as median (inter quartile range-IQR).
Results
46 superobese Emirati patients (27 males and 19 females) who underwent BS (38 laparoscopic sleeve gastrectomy-LSG, 5 Roux-en-Y-gastric bypass-RYGB and 3 multiple surgeries) were identified. Age and BMI before surgery were 34.2 (16.6–57.2) years and 55.8 (50.0–89.9) kg/m^2, respectively. The super obese patients showed significantly higher weight loss compared to patients with BMI between 30 and 45 kg/m^2 [38.9 (31.9–46.1)% v (29.3 (24.0–35.3)%, $P<0.001$]. Patients who underwent LSG had significantly more weight loss in the first year compared to those who underwent RYGB. Weight regain was evident from 18 months onwards in the LSG group while the RYGB group continued to lose and maintain the lost weight up to five years ($P=$ NS).
Conclusion
Our results suggest that among the superobese, BS is more efficacious for weight loss in relative and absolute terms and that RYGB was more effective than LSG for long-term weight loss and maintenance.

DOI: 10.1530/endoabs.65.P227

P228

Investigating mesenchymal stromal cell mediated support of islets after exposure to transplantation related stressors

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The success of islet transplantation in the treatment of type 1 diabetes has been limited by the progressive decline in islet function and viability during isolation and post transplantation. The aims of the current study were to investigate the capacity of a multifunctional progenitor cell type, mesenchymal stromal cells (MSCs), to improve islet insulin secretory function and viability after exposure to transplantation relevant stressors. Mouse islets were cultured with low (IL-1β, 1 ng/ml; TNF-α, 5 ng/ml; IFN-γ; 5 ng/ml) or high (IL-1β, 20 ng/ml; TNF-α, 100 ng/ml; IFN-γ, 100 ng/ml) concentrations of mixed cytokines 24 h or incubated in hypoxic conditions (1% O_2) for 16 h before being cultured with mouse bone marrow-derived MSCs for a further 48 h. Exposure to hypoxia significantly reduced glucose-stimulated insulin secretion (GSIS) ($P<0.01$) and islet cell viability ($P<0.05$). Co-culture of islets with MSCs did not rescue GSIS but did prevent the hypoxia-induced reduction in cell viability ($P<0.01$). Preculturing islets with low concentrations of cytokines did not affect islet cell viability but significantly reduced GSIS ($P<0.001$), which was partially restored by co-culture with MSCs ($P<0.05$). Preculturing islets with higher concentrations of cytokines induced a significant decrease in cell viability ($P<0.01$) which was prevented by co-culture with MSCs ($P<0.01$). Higher concentrations of cytokines also increased insulin release at both basal and stimulatory concentrations of glucose ($P>0.01$), most likely due to β-cell damage since this insulin release was reduced by MSC co-culture in parallel to the improved islet cell viability. These data demonstrate that MSCs can protect islets against hypoxia and cytokine-induced cell death and partially rescue cytokine-induced changes in insulin secretory function. Understanding the mechanisms behind these beneficial effects may allow the development of a cell-free approach to supporting isolated islets and improving clinical islet transplantation protocols.

DOI: 10.1530/endoabs.65.P228

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Steroid deconjugation by helix pomatia – can we overcome snail speed?

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Gas chromatography–mass spectrometry (GC–MS) has been used for urinary steroid analysis for over 50 years. The process of hydrolysis to release steroids from their conjugates is routinely performed using commercially available snail Helix-Pomatia sulfatase (HP). However, as this is a naturally occurring enzyme its production process results in batch variation and so each batch requires experimental validation to adjust for the difference in efficiency of the enzymatic hydrolysis. Thus, a more efficient and consistent solution would be desirable. Steroid conjugates were hydrolysed firstly in 1 ml of pooled healthy male urine. The urine underwent C18 solid-phase-extraction (SPE), followed by enzymatic hydrolysis using either an optimised protocol for HP deconjugation (Sigma-Aldrich, UK) or a synthetic β-Glucuronidase/Sulfatase mix (BGS) enzyme (Kura Biotec, Puerto Varas, Chile). Then a second SPE followed by a two-step methyloxime-trimethylsilyl derivatization (MO-TMS) process. Samples were then analysed by GC–MS using an Agilent 5975 instrument (SIM mode) for steroid identification and quantification, followed by comparison of urinary steroid outputs from the two different enzyme hydrolysis methods. The BGS hydrolysis method involved a shorter incubation (30-min) than HP (3-h). HP and BGS performed equally for all examined glucuronides. For monosulfates, BGS showed a lower deconjugation ability ranging from 35 to 60% compared to the HP. Unlike HP, BGS did not efficiently hydrolyse 21-sulphated hydroxyls or 16β-and-17β sulphates. Under recommended hydrolysis conditions BGS had reduced ability to deconjugate delta-5-sulphated steroids; approximately a third of that observed with HP. The new synthetic-combined BGS performed well for glucuronides but further optimisation of enzymatic hydrolysis conditions is required to maximise delta-5 steroid recovery.

DOI: 10.1530/endoabs.65.P229

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Acute changes in steroid biosynthesis in patients following severe trauma: the golden hour study

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Advancements in medical care have significantly improved survival rates following major traumatic injury. An understanding of the hormonal, inflammatory and metabolic changes that occur following trauma is still evolving but it is clear that they impact significantly upon patient prognosis. To date, studies that have examined trauma-induced changes in steroid metabolism have analysed samples taken from patients post-hospital admission, culminating in marked variability in the time to first blood sample. Here, via the analysis of pre-hospital blood samples acquired within one hour of injury, we have examined steroid biosynthesis in the immediate aftermath of major trauma. We recruited 30 male trauma patients (mean age 26 years; S.D. ±10 years; range 19–59 years) who had an initial blood sample taken within one hour of injury, with subsequent samples taken 4–12 and 48–72 hours post-injury. Blood samples were taken before the administration of analgesics. Morning serum samples obtained from 35 healthy male volunteers (mean 30 years; S.D. ±9; range 18–50) served as a control cohort. Steroids were quantified by liquid chromatography-tandem mass spectrometry on a Waters Acquity UPLC chromatography system coupled to a Waters Xevo-XS mass spectrometer and electrospray ionisation source (positive mode). We quantified 18 steroids including glucocorticoid precursors (progesterone, 17-hydroxyprogesterone, 11-deoxycortisol), glucocorticoids (cortisol, cortisone), mineralocorticoid precursors (11-deoxycorticosterone, corticosterone), the major mineralocorticoid aldosterone, classic pathway androgens (dehydroepiandrosterone (DHEA), DHEA sulfate, androstenedione, testosterone, 5alpha-dihydrotestosterone), and 11-oxygenated androgens (11-hydroxyandrostenedione, 11-ketoandrostenedione, 11-ketotestosterone, 11-hydroxytestosterone). Within minutes of traumatic injury, we observed a steep increase in glucocorticoid and mineralocorticoid outputs while in parallel circulating concentrations of androgens and 11-oxygenated androgens decreased sharply; this steroid profile was sustained at subsequent time points. The relationship of these changes with patient outcome warrants further investigation.

DOI: 10.1530/endoabs.65.P230

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Mammary adipose tissue steroid activation and its relevance for breast cancer prognosis

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Background
Adipose tissue dysfunction could partially explain the well-demonstrated association between obesity and survival in breast cancer (BC). Oestrogen and glucocorticoid concentrations and their respective activation enzymes, oestrogenic 17β-hydroxysteroid dehydrogenases (17βHSDs) and aromatase, and 11βHSD1 are increased in adipocyte hyperplasia and hypertrophy, supporting the hypothesis of a potential role for locally generated steroids in obesity-associated BC. The purpose of this study was to assess the relationships between oestrogens (oestradiol, oestrone) and the inert substrate and active product of 11βHSD1 (cortisone and cortisol, respectively) in breast adipose tissue with adiposity and BC prognostic factors.
Methods
Mammary adipose tissue was collected with ethical approval in pre- and postmenopausal women undergoing partial mastectomy for treatment of BC ($n=17$) or reduction mammoplasty ($n=6$). A validated liquid chromatography-tandem mass spectrometry method was developed to determine oestrogen and glucocorticoid amounts in adipose tissue. Hormone levels differences were assessed using Student's test. Mixed-models were computed to test the association between prognostic factors and hormonal levels.
Results
Oestrogens and glucocorticoids were reliably quantified in mammary adipose tissues (200 mg). Oestradiol, cortisone and cortisol were negatively associated with tumour size ($P<0.05$). The cortisol-to-cortisone ratio was negatively associated with tumour stage ($P<0.05$) independently of BMI, suggesting a decreased activity of 11βHSD1. Women with hormone receptor-positive tumour had higher oestradiol and oestrone levels than women with hormone receptor-negative tumour ($P<0.05$). Ratio of oestradiol-to-oestrone was higher in lean women compared to women with a BMI ≥ 25 kg/m^2 ($P<0.05$), suggesting little impact of 17βHSDs conversion per mass unit in adipose tissue in obese BC.
Conclusions
Oestrogens and glucocorticoids were detected in breast adipose tissue healthy women as well as those suffering from BC. Oestrogens levels, but not glucocorticoids levels, were negatively associated with adiposity. Our findings suggest that smaller breast tumours are associated with higher levels of oestradiol, cortisone and cortisol in adipose tissue.

DOI: 10.1530/endoabs.65.P231

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Anti thrombin activity in newly diagnosed Type 2 diabetes subjects in a Tertiary Hospital in Calabar, Nigeria

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Introduction
Vascular complications play a significant role in the morbidity and mortality associated with diabetes mellitus (DM). Eighty percent of deaths in patients with

diabetes are related to thromboembolic complications. Significant alteration in haemostatic indices have been documented in these patients. However, this has not been investigated in our environment.
Objectives
This study aims to evaluate antithrombin activity (AT) in newly diagnosed subjects with diabetes; to determine the prevalence of AT deficiency in them; to test the association between AT deficiency and vascular complications in diabetes and to correlate AT activity with body mass index and haematological indices in the newly diagnosed diabetes subjects.
Methodology
This is a cross sectional study conducted at the University of Calabar Teaching Hospital, Calabar. Sixty newly diagnosed DM subjects were recruited consecutively from the DM Clinic and 54 non diabetic controls were recruited from the general population. Venous blood was collected into citrate specimen container and ethylenediaminetetracetic acid (EDTA) containers for determination of AT activity and haematological indices respectively. AT activity was determined with technoclone chromogenic AT kit and Full Blood Count was analyzed using an automated hematology analyzer. Result was analyzed with the statistical package for social science version 16.
Result
The mean AT activity in newly diagnosed diabetes subjects was significantly lower than in controls (83.3 ± 30.0 vs. 92.8 ± 20.0; $P = 0.050$). The prevalence of AT deficiency in newly diagnosed DM subjects was 32.3%. AT deficiency was associated with overweight/obesity (BMI >25 kg/m^2) and thrombocytopenia (platelet count $<150\times10^9$ cells/l). Microvascular complication was associated with AT deficiency. There is a statistically significant negative correlation between BMI and AT activity ($r = -0.276$; $P = 0.030$).
Conclusion
Antithrombin activity is significantly reduced in newly diagnosed DM subjects and it is associated with microvascular complications.

DOI: 10.1530/endoabs.65.P232

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L-Phenylalanine simulates the secretion of pancreatic hormones via vagal CaSR

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High protein diets are effective at promoting weight loss and stimulating the secretion of pancreatic hormones. Understanding the mechanisms underlying these effects may highlight new potential therapeutic targets. The calcium sensing receptor (CaSR) is stimulated by calcium and plays a critical role in calcium homeostasis. However, it is also found in many tissues unrelated to calcium regulation. CaSR activity can be modulated by aromatic amino acids, most potently by L-Phenylalanine, and CaSR has been suggested to act as a nutrient sensor mediating some of the physiological effects of protein intake. Previous work from our group found L-Phenylalanine drives anorectic gut hormone release and satiety, partly via the CaSR. Oral administration of L-Phenylalanine to mice also stimulates the secretion of the pancreatic hormones, insulin and glucagon. However, the mechanisms underlying these effects are unclear. The vagus nerve sends both afferent sensory and efferent motor signals between the brain and peripheral organs such as the gut and pancreas. Interestingly, vagal sensory afferents express the CaSR. Orally administered L-Phenylalanine stimulated c-Fos like immunoreactivity in the brainstem of mice and rats, the site of vagal innervation. Additionally, CaSR synthetic agonists modulate vagal activity *in vitro*. Using mice with a floxed CaSR gene and injecting cre expressing adeno-associated virus into the nodose ganglia, where the cell bodies of vagal afferents reside, we were able to selectively knockdown CaSR expression in the vagus nerve. This had no effect on L-Phenylalanine's anorectic effects, but blunted L-Phenylalanine's ability to stimulate glucagon secretion. This suggests that vagal CaSR may play an important role in mediating amino acid induced pancreatic hormone secretion. Further studies are required to determine the importance of vagal CaSR in the regulation of pancreatic hormone secretion, and whether this pathway is conserved in humans and can be exploited to develop novel anti-diabetic therapies.

DOI: 10.1530/endoabs.65.P233

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Adhesion G-protein coupled receptors as novel players in islet development

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Adhesion GPCRs (aGPCRs) have been implicated in developmental processes and deletion of some aGPCRs in neonatal mice results in decreased β-cell differentiation capacity, leading to glucose intolerance in adult life. Here, we investigated the expression of aGPCR mRNAs in mouse islets and determined the expression and function of GPR56, the most abundant aGPCR in islets, in developing mouse pancreas. Quantitative PCR indicated that mouse islets expressed mRNAs encoding 26 of the 32 aGPCRs, with GPR56 being the most abundant of all islet aGPCRs, while 8 were expressed at only trace levels. GPR56 expression was approximately 15-fold higher than the next most highly expressed aGPCRs: CELSR1, GPR125, ELTD1 and LPHN1. RNAscope *in-situ* hybridization and immunohistochemistry revealed that GPR56 was strongly expressed by SOX9- and NGN3-positive mouse pancreas endocrine progenitors, with significantly increased expression at post-natal day 9 (P9), where beta-cell replication peaks (% area GPR56$^+$ cells; E18: 0.15 ± 0.05, P9: 0.47 ± 0.07, $n=10$, $P<0.01$). In islets from P9 GPR56 knockout (KO) mice, the number of cells proliferating and remaining in the cell cycle was significantly lower than in age-matched WT mice (BrdU+Ki67+ cells/μm^2; WT: 115.9 ± 18.2, KO: 50.9 ± 6.3, $n=3$, $P<0.05$), leading to less β-cells at this stage (% β-cells/islet; WT: 68.5 ± 0.8, KO: 54.8 ± 3.0, $n=3$, $P<0.05$), but higher numbers of α-cells in GPR56KO islets (% α-cells/islet; WT: 17.7 ± 0.9, KO: 33.7 ± 2.8, $n=3$, $P<0.01$). Our data support an important role for the abundant aGPCR GPR56 in islet development, indicating that it is required for an appropriate α-/β-cell ratio.

DOI: 10.1530/endoabs.65.P234

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Insights into the mechanisms underpinning the physiological effects of biased GLP-1 receptor agonists

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Glucagon-like peptide-1 receptor (GLP-1R) agonists are effective treatments for type 2 diabetes and obesity. We recently described 'biased' peptide GLP-1R agonists modelled on exendin-4 which uncouple the pronounced endocytosis that usually accompanies GLP-1R activation, leading to prolongation of intracellular signalling responses. Here, we show that the metabolic consequences of biased GLP-1R activation *in vivo* are dominated by improvements in blood glucose, without concomitant increases in their anorectic properties (40-fold relative preference for glycaemic vs. anorectic effects). To investigate this disparity, we have compared cell type-specific responses to biased GLP-1R agonists using *in vitro* beta cell and neuronal models, in case the downstream manifestations of bias differ according to the tissue in which they act. We also delivered these ligands directly into the CNS in mice to bypass the blood-brain-barrier, under which circumstances the anticipated efficacy increase of the biased agonist was restored. Biodistribution studies using the same compounds conjugated to near-infrared fluorophores, which allow deep tissue imaging of optically cleared intact brain and pancreas specimens, have also provided a means to assess whether biased ligands have equal or differential access to appetite regulatory centres in the CNS.

DOI: 10.1530/endoabs.65.P235

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Case reports of immunosuppression therapy for anti-insulin receptor and anti-insulin antibodies in patients attending the national severe insulin resistance service

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Introduction
Immune mediated cases of severe insulin resistant diabetes are very rare. We report responses to immunosuppression with rituximab in two patients.
Case 1
A 31 year old black African female, BMI 22.84 kg/m^2, was referred with new onset diabetes, diagnosed shortly following a miscarriage. She had weight loss, acanthosis nigricans, nocturnal hypoglycaemia and severe hyperandrogenism . She was on an insulin pump and required >1000 units insulin per 24 h. Fasting insulin 4749 pmol/l, leptin 1.2 ug/l, normal lipids, HbA1c 83 mmol/mol (9.7%). Immunoprecipitation studies confirmed the presence of anti-insulin receptor antibodies. Rituximab infusions were given 6 monthly for two years. After two doses of rituximab, she had gained 13 kg, required no diabetes medication, her HbA1c was 33 mmol/mol and insulin 59 pmol/l. She reported no further hypoglycaemia and was back at work.
Case 2
A 64 yr old Asian male, BMI 24.91 kg/m^2, with sub-optimally controlled type 2 diabetes treated with porcine insulin. Reported multiple insulin intolerances. Frequent episodes of hyper/hypoglycaemia. No response to previous steroid or mycophenolate. No acanthosis nigricans or features of lipodystrophy. Fasting insulin >100 000 pmol/l, triglycerides 2.4 mmol/l, HbA1c 102 mmol/mol (11.5%). Anti-insulin antibodies were detected at a high titre and further analysis confirmed these were functional antibodies. Rituximab therapy was commenced. One month post first dose rituximab insulin doses were reduced, HbA1c 93 mmol/mol (10.7%), fasting insulin 79 920 pmol/l. This initial improvement is encouraging and further improvement is expected.
Conclusion
In patients with insulin resistant diabetes, especially those with intermittent hypoglycaemia, consider immune mediated causes of resistant diabetes as this is potentially reversible with immunosuppressive therapy.

DOI: 10.1530/endoabs.65.P236

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Obesity induces cardiac hypertrophy without functional or fibrotic alterations

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Background
Cardiac fibrosis is a common biological response to cardiovascular injury. Maladaptive cardiac fibrosis as observed in patients with hypertension, obesity or diabetes mellitus contributes to contractile dysfunction and electrophysiological disorders. Currently, there is controversy regarding whetherexposure to a high fat diet (HFD) in isolation induces cardiovascular damage and fibrosis. Here, we set out to explore the contribution of different models of obesity to the development of cardiac fibrosis and cardiovascular remodeling.
Methods
C57BL/6 mice were fed standard chow diet or HFD (60% fat from lard) for 20 and 30 weeks. Adult *Ob/Ob* mice (genetic model of obesity) were also studied. Mice subjected to severe transverse aortic constriction (sTAC, 28 G needle) for 3 weeks were used as positive control for fibrosis. Fibrosis development was assessed by histological analyses using Masson's Trichrome and Picrosirius red staining. The levels of fibrosis markers (mRNA and protein) of collagen I, collagen III and fibronectin were determined by RT-qPCR and Western blot. Myocardial function was assessed by echocardiography.
Results
Increased insulin levels, glucose intolerance and obesity were observed after 20 weeks of HFD. However, we did not observe changes in myocardial function (systolic) nor myocardial fibrosis. Long-term exposure to HFD for 30 weeks did not elicit differences in glucose tolerance, myocardial function or cardiac fibrosis. Similar results were observed in the genetic model of obesity. Meanwhile, severe pressure overload model (sTAC) triggered heart failure with reduced ejection fraction and cardiac fibrosis.
Conclusions
These results suggest that myocardial fibrosis observed in patients with metabolic diseases (e.g. obesity and diabetes) requires the presence additional comorbidities (e.g. afterload stress, endothelial damage).

DOI: 10.1530/endoabs.65.P237

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Idiopathic gigantomastia: newer mechanistic insights implicating the paracrine milieu

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Objective
The primary objective was to characterise the paracrine milieu in three subjects with apparently idiopathic gigantomastia and to study the relative expression of implicated factors in these pathological specimens as compared to tissue samples from normal breast, gynecomastia and breast cancer.
Background
Gigantomastia refers to pathological breast enlargement usually occurring in the peripubertal or peripartum period. Idiopathic gigantomastia, however, is a rare entity with hypotheses citing local expression of hormones and growth factors in causing this disease, none of which have been systemically analysed. The purpose of this study was to delve deeper into the mechanistic pathways causing this condition.
Design
Three subjects with gigantomastia unrelated to puberty or pregnancy were found to be negative for known causes for the same. Hence, they were subjected to reduction mammoplasty in one and core biopsy in the other two patients. Histopathological examination and immunohistochemistry for ER, PR and Her-2-Neu were performed in all specimens. Quantitative immunofluorescence for aromatase, IGF2, EGFR, TGF-β, PDGFR-a, β, IGF1 and PTHrP was performed not only in patient samples but also in representative tissue from normal breast, benign (gynecomastia) and malignant(breast cancer) specimens. Relevant positive and negative controls were used for validation.
Results
Herein, we describe three patients of idiopathic gigantomastia, including a postmenopausal female. Both are extremely rare and there are only few studies that have attempted to characterise their etiopathogenesis. Serum markers of autoimmunity, incriminated hormones and growth factors analysed, were normal in all the cases. Tissue expression of aromatase, IGF2, EGFR, TGF-β, PDGFR-a and β were found to be upregulated whereas IGF1 and PTHrP were comparable to normal breast.
Conclusion
The observation that paracrine overexpression of these factors is responsible for the pathogenesis of apparently idiopathic gigantomastia may have therapeutic ramifications in the future for patients with this debilitating condition.

DOI: 10.1530/endoabs.65.P238

P239

Weight loss and change in obesity related comorbidities in patients undergoing laparoscopic adjustable gastric banding at UHCW between 2009 and 2012

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Background
The Royal College of Physicians (RCP) called earlier this year for obesity to urgently be recognized as a disease, and warned that until this happens its prevalence is unlikely to be reduced. Obesity is associated with multiple comorbidities, including type 2 diabetes mellitus (T2DM), hypertension (HT), and dyslipidemia. Bariatric surgery (BS) produces dramatic weight loss, with improvement of obesity associated comorbidities and decrease of overall mortality.
Objectives and methods
The aim of this study was to evaluate the impact of weight loss on obesity associated comorbidities 1, 2 and 5 years following BS. 91 severely obese patients (81.3% women, mean age 44.5 ± 10 years, mean BMI 51.6 ± 5.2 kg/m^2) underwent laparoscopic adjustable gastric banding (LAGB) between February 2009 and June 2012. Results obtained 1, 2 and 5 years postoperatively were compared to the preoperative values using SPPS software version 20.
Results
A significant drop in BMI was recorded throughout the follow-up period, as well as in HbA1c, with greatest improvement seen 2 years after surgery (51.6 ± 5.2 kg/m^2 vs. 40.1 ± 6.5 kg/m^2, $P < 0.05$ and 58.7 ± 18.8 mmol/mol vs. 43.3 ± 14.5 mmol/mol, $P < 0.05$). In addition, positive results were noted when analyzing the change in treatment. After 5 years, the percentage of patients using glucose lowering agents declined (47.1% vs. 30.6%, $P < 0.05$), and patients were taking less antihyperlipidemic drugs compared to baseline (41.9% vs. 28%, $P < 0.05$). However, the reduction of antihypertensive medication use, was non-statistically significant (67.4% vs. 57.1%, P = ns).
Conclusions
LAGB is an effective procedure producing significant and durable weight loss, with maximum effect obtained 2 years after surgery. Improvement in obesity related comorbidities following LAGB varies. The effect on hypertension control was minimal while both glycemic and lipid status improved, with less medication use postoperatively. Results were maintained after a longer follow up period.

DOI: 10.1530/endoabs.65.P239

P240

Safe use of variable rate intravenous insulin infusion: a trust wide audit

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Aims and objectives
Variable rate insulin infusion (VRII) is commonly used to achieve normoglycaemia in hospitalised patients. Joint British Diabetes Society (JBDS) produced guidelines on VRIII in 2014 to minimise complications related to inpatient VRII use. Local guidance along with a new VRII chart was introduced in 2017 at the West Suffolk NHS Foundation Trust and staff training provided. We performed an audit to review compliance to national and local VRII guidance.
Methods
We conducted a prospective audit on patients receiving VRII at medical and surgical wards for a period of one month. Audit standards included correct indication of VRII, correct duration of VRII, background insulin prescribing, regular electrolyte monitoring and appropriate transition off VRII.
Results
25 patients were identified. The audit demonstrated good compliance with indication of VRII (100%), duration of VRII (100%) and background insulin prescription (100%). Only 60% of patients had daily electrolytes monitoring and 76% were appropriately taken off VRII.
Conclusion
Our trust did well in many areas in comparison with national performance shown by National Diabetes Inpatient Audit (NaDIA 2017). We do, however, need to improve our compliance in appropriate transfer off VRII and daily electrolytes monitoring. We plan to hold a series of staff training events for further education and re-audit in 12 months.

DOI: 10.1530/endoabs.65.P240

P241

Investigating the role of microRNA-7 in pancreatic islet development

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Cadaveric islet transplantation can cure diabetes, however scarcity of donor islets means that this approach cannot be used for large-scale treatment. An alternative source of insulin-producing β-cells or whole islets would be step-wise *in vitro* differentiation from either human embryonic stem cells or induced pluripotent stem cells, which could be transplanted directly into patients. However, 'β-like' cells generated from existing differentiation protocols are produced at very low efficiency and lack numerous markers of functional maturity, indicating that our current understanding of *in vivo* β-cell specification is incomplete. Mice with genetic inactivation of *Dicer1*, a key component of the microRNA (miRNA) biogenesis pathway, show decreased β-cell mass indicating that miRNAs play a crucial role in the differentiation of pancreatic endocrine progenitors during development. miR-7 is highly expressed in pancreatic endocrine cells of the embryo and in mature β-cells of adult mice, suggesting it may be a key factor in driving β-cell specification. Here, we delete the miR-7 gene family in mouse endocrine progenitors using a neurogenin3 (Ngn3)-Cre transgene (NKO). miR-7 will be deleted at the initiation of endocrine specification, at which time Ngn3^{LOW} cells are still capable of acquiring a pancreatic ductal fate. We find that adult NKO mice are hyperglycemic and show reduced α- and β-cell mass. Lineage tracing experiments demonstrated that Ngn3$^+$ progenitors of NKO mice do not leave the epithelial plexus and instead contribute to the developing ductal network. Our results suggest that the miR-7 gene family is a key regulator of cell fate decisions in the pancreas by promoting endocrine differentiation of Ngn3^{LOW} bipotent pancreatic progenitors toward α- or β-cell fates as opposed to a ductal fate. We believe that modulation of miR-7 expression in *in vitro* differentiation protocols may thus be used to increase the efficiency and maturity of β-like cells.

DOI: 10.1530/endoabs.65.P241

P242

Glucocorticoid treatment is associated with dose-dependent effects in healthy male volunteers

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Objective
2–3% of the population of the UK receive glucocorticoid (GC) therapy. Significant adverse effects are not confined to chronic use: recurrent short-course administration is associated with increased morbidity and mortality. Data about the cumulative dose responsible for drawbacks during GC treatment are still lacking. The aim of this study was to test the impact of 7 days of 10 or 15 mg of Prednisolone on metabolism in healthy male volunteers.
Methods
16 healthy male volunteers were recruited from the Oxford Bio-Bank and divided into 2 age- and BMI-matched control groups as following: 6 volunteers received 10 mg of Prednisolone and 10 volunteers received 15 mg of Prednisolone for 7 days. Anthropometric and metabolic parameters were recorded and all patients underwent low dose hyperinsulinaemic–euglycaemic clamp (HEC), before (pre) and after (post) treatment. The main outcome measure was the M-value gathered from the HEC.
Results
Age, BMI and fasting blood glucose were not different between the groups at baseline. After one week of prednisolone 10 or 15 mg, no differences were found in delta (Δ = post-pre) fasting glucose (FG) (median ΔFG_{15mg} 0.15 ± 0.36 nmol/l vs. ΔFG_{10mg} 0.15 ± 0.36 nmol/l, $P = 0.635$). However, M-value was significantly reduced in patients taking 15 mg of prednisolone (median ΔM_{15mg} −2.5 ± 2.0 mg/Kg per min vs. ΔM_{10mg} −0.4 ± 1.3 mg/Kg/min, $P = 0.016$), as well as serum potassium (median ΔK_{15mg} −0.3 ± 0.2 mEq/l vs. ΔK_{10mg} 0.10 ± 0.18 mEq/l, $P = 0.011$). No differences were found in Δcholesterol (total, HDL and non-HDL), liver or kidney function.
Conclusions
In this small cohort of healthy male volunteers, we demonstrated that GC treatment is associated with a worsening of insulin sensitivity through a dose-dependent effect. In addition, the decrease of serum potassium underpin the dose-dependent mineralocorticoid activity of GC. Further studies are needed to confirm our findings in larger cohort of patients.

DOI: 10.1530/endoabs.65.P242

P243

Mass spectrometric characterisation of circulating proinsulin-derived peptides in insulin autoimmune syndrome

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Autoimmune immunoglobulins directed against peptide hormones are well-described. These are often clinically benign, but may cause a deleterious effect on the accuracy of clinical immunoassays. A notable exception is Insulin Autoimmune Syndrome (IAS, also known as Hirata disease), where antibody-binding has a direct effect on insulin kinetics resulting in aberrant glucose control. Current methods to diagnose IAS rely on crude immune-subtraction techniques such as polyethylene glycol precipitation, or cumbersome size fractionation of the immunoreactive species. The most widely-accepted model for IAS, based on data from studies of insulin kinetics, is that autoantibodies delay insulin clearance. Both the hyper- and hypoglycaemic phases in IAS are then explained by the sequestration of insulin followed by delayed clearance. With the advent of high resolution accurate-mass mass spectrometers and the application of peptidomic approaches for data analysis, it is now possible to examine the structural nature of the antibody-bound peptides in IAS with far greater selectivity. Data presented show, in addition to large amounts of insulin, the presence of proinsulin and proinsulin-derived peptides, in the plasma of six patients with IAS. A combination of size-exclusion chromatography and LC–MS/MS analysis show that, as well as insulin and intact proinsulin, two 'des' forms (des 31-32 and des 31–33 − which are partially cleaved proinsulin molecules, the numbered residues absent due to prohormone convertase/carboxypeptidase action) are present in plasma and may be antibody-bound. C-peptide was not present in the antibody-bound fractions. A likely mechanism for the excess of proinsulin and incompletely processed proinsulin species in IAS is one of sequestration by antibody, which, in effect, enriches these species by delaying their clearance rate. As proinsulin, and both des proinsulin forms, have biological activity, they may contribute to hypoglycaemia in IAS, even though are less potent than the mature insulin species.

DOI: 10.1530/endoabs.65.P243

P244

Hepatic steatosis in rats with dexamethasone-induced metabolic syndrome: a role for *Ocimum gratissimum* leaf extract

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Ocimum gratissimum (OG) was shown to reverse dyslipidemia in diabetes mellitus. The present study investigates the effect of OG on hepatic lipid synthesis in animals with metabolic syndrome induced by dexamethasone. Twenty male Wistar rats (130 ± 20 g) were randomly grouped into four ($n=5$ each) as control, normal + OG, Dex and Dex + OG. Dexamethasone (1 mg/kg) was administered intraperitoneally to Dex and Dex + OG groups followed by normal saline and OG (400 mg/kg), respectively; while control and normal + OG were administered normal saline and OG, respectively. Body weight was monitored before and after the treatments. After 10 days of treatments, under anaesthesia by sodium thiopental (50 mg/kg, i.p.), liver was obtained for determination of HMG Co A/mevalonate ratio as a measure of cholesterol synthesis and for histological staining using H and E as well as lipid specific stain. Data were presented as mean ± SEM, compared using ANOVA and post-test analysis at $\alpha_{0.05}$. The result showed marked reduction in body weight of Dex and Dex + OG animals. HMG Co A/mevalonate ratio was significantly decreased in the Dex but increased in the Dex + OG compared with control, thus cholesterol synthesis which was increased in the Dex was significantly decreased in the Dex + OG since an inverse relationship exist between HMG Co A/mevalonate ratio and cholesterol synthesis. Hepatic steatosis was widely spread in the Dex but significantly cleared in the Dex + OG. It was concluded that treatment with OG significantly inhibits hepatic cholesterol synthesis.

DOI: 10.1530/endoabs.65.P244

P245

Glycaemic control in patients with diabetes mellitus in a Tertiary Hospital in South-West, Nigeria

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Background
Diabetes Mellitus (DM) is a metabolic disorder characterized by elevated blood glucose with accompanying microvascular and macrovascular complications resulting in increased morbidity, mortality and reduce quality of life in an individual living with the disease. Studies have shown that tight glycaemic control contributes immensely to the reduce risk of microvascular complications, and to a certain extent macrovascular complications. Achieving tight glycaemic control is an important factor in the management of DM.
Objectives
The study aimed to assess the glycaemic control in diabetes patients attending diabetic clinic in a tertiary hospital in south-West, Nigeria, using American Diabetic Association criteria for glycaemic target (HbA1c < 7%, Fasting blood glucose = 4.4–7.2 mmol/l).
Method
This cross-sectional study involved 212 subjects with DM, registered and already receiving treatment for diabetes for at least one year in a tertiary hospital, in South-West, Nigeria. Participants were interviewed using a structure proforma. Glycaemic control was assessed by measuring level of glycated haemoglobin (HbA1c) and fasting blood glucose (FBG). Data was analyzed using Statistical Package for Social Sciences version 22.0.
Results
The mean age of participants was 59.6 ± 12.3 years. Female constituted 65.1% of the study population while 34.9% were male. The mean fasting blood glucose was 8.2 ± 2.5 mmol/l while the mean level of glycated haemoglobin was 8.7 ± 2.3 %. About a third (34%) of the study populations had HbA1c less than 7% while 42% had FBG between 4.4 and 7.2 mmol/l. Two participants had FBG < 4.4 mmol/l.
Conclusion
This study has demonstrated that poor glycaemic control is common among individual with DM. there is need to intensify diabetic education targeting benefit of good glycaemic control with the aim of preventing DM complications and reducing morbidity and mortality from the disease.
Keywords
Glycaemic control, Diabetes Mellitus, Glycated haemoglobin, Fasting blood glucose

DOI: 10.1530/endoabs.65.P245

P246

Presentation, investigations and management of suspected Gitelman syndrome in pregnancy

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G2, P1, IUGR in previous pregnancy. Presented in 34/40 of pregnancy with profound lethargy, muscle weakness and fatigue. Found to have normotensive hypokalaemia − 2.6 mmol/l and mild metabolic alkalosis. No preceding vomiting, diarrhoea or nutritional cause. Pre-natal blood results were not available but reported low K^+ in 2009. Required intravenous potassium replacement and symptoms improved dramatically with restoring normokalaemia. Results at diagnosis: K+ 2.6 mmol/l, Na − 131 mmol/l, pH − 7.5, bicarbonate − 31.2 mmol/l, magnesium 0.8 mmol/l, renin − 156 mU/l, aldosterone − 3930 pmol/l, 24-h urine collection for calcium and magnesium unfortunately not returned despite prompting. Diagnosis of Gitelman syndrome (GS) was made in the absence of alternative cause. Potassium replacement (Sando K 2 tablets tds) continued for the rest of pregnancy with close K^+ monitoring (3.5−4.7 mmol/l). Pregnancy progressed well and growth scans were normal. Underwent IOL at 39/40 and delivered heathy baby (baby's potassium − 3.7 mmol/l). Patient' s potassium in labour fell to 2.7 mmol/l despite period of stability and stable Sando K dose prenatally and required iv replacement and ECG monitoring in labour.
Discussion
Diagnosis of GS in pregnancy is difficult as biochemistry seen in GS such as rise in renin and aldosterone and increased renal filtration rate, also occur as physiological changes in pregnancy especially in third trimester. Pregnancy in GS is mostly uneventful but association with IUGR, miscarriage and oligohydramnios has been reported. Hypokalaemia can worsen in pregnancy and K^+ therefore

needs to be closely monitored and supplement dosing may need adjustment. Hyperventilation and anxiety in labour can exacerbate severe hypokalaemia. It is important that the obstetrics team and anaesthetist are aware of the diagnosis as potential issues intrapartum can include arrhythmias, laryngospasm and tetany provoked by K^+ drop.

DOI: 10.1530/endoabs.65.P246

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Audit on initial investigation and management of hyponatraemia in inpatients

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Background
Hyponatraemia is encountered in 15−20% of inpatients but remains suboptimally managed. It leads to increased morbidity, length of stay and mortality. A closed-loop audit on investigating and managing inpatients with hyponatraemia was conducted, to identify pitfalls in management.
Method
A retrospective audit of general medical inpatients admitted over three months with a serum sodium level of less than 130 mmol/l was conducted. Relevant initial and follow up investigations and outcomes were reviewed. Subsequent interventions included teach-in sessions for doctors and nurses as well as raising awareness through posters with an algorithm for investigation and management of hyponatraemia displayed in the wards. The audit was repeated after four months.
Results
There were 17 patients (mean age 74 years) in the first audit and 14 patients (mean age 76 years) in the second. The re-audit showed that volume status assessment improved from 65% to 78%. Fluid balance or daily weight recording improved from 17% to 71%. The use of appropriate further biochemical investigations (such as paired urine and serum osmolalities, urine sodium, cortisol and thyroid hormone levels) improved from 6% to 42%. Improvement in serum sodium levels in the first 24 h was similar in the two audits (82% vs.85%) and levels in all patients in both audits increased but not more than 10 mmol/l in 24 h. Mean length of stay was 9 days in the first audit and 11 days in the second. Mortality rates were 3/17 and 4/14 in the first and second audits respectively.
Conclusions
Management of hyponatraemia remains challenging but can be improved by raising awareness and through education. A local guideline is currently under development to facilitate this. Outcomes are more difficult to influence, which may reflect a cohort of older patients with co-morbidities.

DOI: 10.1530/endoabs.65.P247

P248

Using problem-based learning (PBL) to engage undergraduate medical students in endocrinology at Edinburgh Medical School

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Background
Endocrinology, taught in Year 2 of the Edinburgh undergraduate MBChB curriculum to approximately 200 medical students, can present a complex challenge and a test of engagement. Core biomedical curriculum content is delivered as large group teaching (lectures) and then revisited in smaller groups (clinical-cased based tutorials, PBL) designed to integrate learning by applying basic knowledge in a clinical context. PBL first implemented in the 1960s at McMaster University Medical School by Barrows and Tamblyn, is a small group student-centred pedagogy in which students manage their own learning while practicing collaborative and empathetic skills. The aim in Edinburgh is to make the endocrine curriculum engaging and memorable through delivery of a PBL casebook of illustrative scenarios.
Methods
A series of vertically integrated endocrine scenarios covering gut-brain, thyroid, calcium, diabetes, hypothalamus−pituitary and reproduction have been developed as PBL cases delivered to students contemporaneously with relevant lecture and tutorial course material. For quality assurance, both the generic PBL case performance and specific student endocrine experience are evaluated each academic year by Likert five-point scale and free text response questionnaires.
Results
Responses to endocrine PBLs (2019–19 assessment) returned mainly five (definitely agree) and four (mostly agree) point anchors. Students considered that PBL '…reinforces biomedical science material' (36.7%/56.7%) and '…provokes discussion' (33.3%/46.7%). In addition, PBL scenarios'… help search and research the evidence base' (34.8%/56.6%), '… develop critical appraisal skills' (26.1%/47.8%) and '…help me feel comfortable in first formulating, and second voicing ideas…' (43.5%/43.5%). Crucially, quantitative data analysis allows comparison with previous years' experience and appraisal of new or modified cases.
Conclusion
Endocrine PBL is highly rated by students as an opportunity to make learning memorable by applying and reinforcing basic biomedical knowledge in a more clinical context, promoting critical thinking and modelling clinical behaviour, while highlighting the patient-centred nature of the case scenarios.

DOI: 10.1530/endoabs.65.P248

P249

'H' syndrome; a rare case with novel symptoms

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Background
'H' syndrome is a rare autosomal recessive disorder characterised by hyperpigmentation, hypertrichosis, hepatosplenomegaly, hearing loss, hypogonadism, hyperglycaemia (insulin-dependent diabetes), hallux valgus and low height (short stature) and systemic inflammation. Caused by mutations in SLC29A3 gene located on chromosome 10q23 which encodes the human equilibrative nucleoside transporter 3 (hENT3). We report this case to highlight the rarity of the Syndrome with plethora of unusual symptoms.
Case
A 23 year old lady presented with primary amenorrhoea and poorly controlled diabetes with a HbA1c 9%. Born to non-consanguineous parents of Asian descent she had significant complaints at various stages of her life. Early childhood was marked with delayed mile stones, and recurrent pneumonia. She was diagnosed with Insulin dependent Diabetes (IDDM) at puberty and was initiated insulin therapy, also evaluated for lack of pubertal changes. Examination findings were remarkable with pallor, hypertelorism, well defined symmetrical hyperpigmentation on abdomen and bilateral inner thighs, hypertrichosis, short stature, hypogonadism (Tanner stage 2), hepatosplenomegaly, hallux valgus, sensory neural hearing loss and arcus senilis. Laboratory investigations revealed Microcytic anaemia, hyperglycemia, positive anti-GAD antibodies and anti-Insulin antibodies, Subclinical hypothyroidism, low normal FSH and LH, normal morning cortisol and a negative ANA profile. Ultrasound abdomen findings which were confirmed on CECT revealed hepatosplenomegaly, shrunken pancreas, renal parenchymal changes, hypoplastic uterus, PCOD and retroperitoneal fibrosis. Treatment with immunosuppressants showed significant symptomatic improvement especially auto-inflammatory conditions.
Conclusion
H Syndrome is a rare disorder giving rise to unusual debilitating symptoms at various stages of life. Biopsies from involved skin showed that it as a form of inherited histiocytosis. Treatment with immunosuppressants appears to be promising. Potential manifestations such as hypogonadism and pancreatic insufficiency call for ongoing attention of the Endocrinologist, however, multidisciplinary care is inevitable for the long term management.
Keywords
H syndrome, SLC29A3, hypertrichosis, retroperitoneal.

DOI: 10.1530/endoabs.65.P249

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Abstract withdrawn.

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Five-year review of diabetic foot ulcer admissions at Obafemi Awolowo University Teaching Hospital, Ile-Ife, Nigera

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Background
Diabetic foot disease is a major cause of morbidity and mortality in people living with diabetes. It is a leading cause of minor or major limb loss with attendant huge economic ruins.
Objective
The aim of the study was to determine pattern of presentation of diabetic foot ulcer (DFU), assess co-morbid conditions at admission and determine the overall outcome of patients managed over the 5 year study period.
Materials and methods
The study design was a retrospective study of all diabetic foot ulcers admitted to the medical wards of OAUTHC Ile-Ife between 2011 and 2015. Case notes were reviewed to obtain data on socio-demographic indices, duration of DM, treatment outcome, blood glucose at presentation and DFU was graded using the Wagner's grading at admission. Laboratory investigation results done at presentation or during admission were noted. Treatment outcome was categorized into patients discharged, deceased or discharged against medical advice. Data obtained was analyzed using SPSS 20.
Results
68 Case notes were retrieved, and these were made up of 27 (39.7%) males and 41 (60.3%) females. Mean age was 54.6 years and 58.7 years for male and female subjects respectively. Males presented with longer duration of diabetes and ulcer. Average blood glucose at presentation was 18 mmol/l with PCV average of 30% for both sexes. One (1.5%), five (7.4%), 15 (22.1%), 33(48.5%) and 6(8.8%) patients presented with Wagner's grade 1, 2, 3, 4 and 5 respectively; 8(11.7%) ulcers were not graded. Mortality was 30.9% among the reviewed cases.
Conclusion
Mortality from diabetic foot ulcer remains regrettably high despite advances in diabetes management. There is the need for aggressive and comprehensive diabetic education to stem the tide of this largely preventable cause of physical, emotional and financial losses.

Keywords
Diabetes Mellitus, Diabetic Foot Ulcer, Wagner's, Mortality
DOI: 10.1530/endoabs.65.P251

P252

Molecular interactions of cashew leaf (*Anacardium occidentale*) derived compounds with anti-diabetic targets: *in silico* and *in vivo* studies

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Anacardium occidentale (cashew tree) belongs to the Anacardiaceae family and has been well used in folklore medicine for the treatment of various ailments such as gastrointestinal disorders, hypertension and diabetes. Literature is replete with reported anti-diabetic actions of cashew leaf. The molecular mechanism of the hypoglycemic activity of *A. occidentale* was investigated in this study. Insulin, Glucagon like peptide-1 (GLP-1), dipeptidyl peptidase-4 (DPP-4) and marker of proliferation KI67 (MKI67) gene modulation by *A. occidentale* was investigated *in vivo* by RT-PCR and possible compounds responsible for anti-diabetic action predicted through *in silico* approach. Phytochemicals previously characterized from *A. occidentale* through GC−MS analysis were docked into glutamine fructose-6-phosphate amidotransferase (GFAT), glucagon like peptide-1 receptor (GLP-1r), dipeptidyl peptidase (DPP-4) using Autodock Vina. *In silico* findings suggest alphacadinol (ligand for DDP-4 and GFAT) and betacaryophylene (ligand for GLP-1r) as the major anti-diabetic compounds in cashew leaf. *In vivo* study showed increase in GLP-1, insulin and MKI-67 expression in *A. occidentale*-treated rats compared to the controls. This study indicates that the underlying molecular mechanisms of the actions of these compounds is through activation of insulin and GLP-1 receptor. This work confirmed the use of this plant in diabetes management and the probable bioactive components eliciting anti-diabetic effects are alphacadinol (a sesquiterpenoid) and betacaryphylene (a sesquiterpene) and both belong to the class of terpenes.

DOI: 10.1530/endoabs.65.P252

P253

Juvenile type 2 diabetes and Klinefelter syndrome

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Introduction
Klinefelter Syndrome (KS) is the most common male sex-chromosome abnorrmality, typically presenting with features of hypogonadism. The association between KS and Type 2 Diabetes is not fully understood as early treatment with testosterone does not minimise this complication. We present an unusual case of simultaneous diagnosis of T2DM and Klinefelter Syndrome in a young adult.
Case
A 17 year old Pakistani gentleman presented with a short history of osmotic symptoms, hyperglycaemia and weight gain. Medical history included beta-thalassaemia trait and family history of T2DM. Venous glucose was 17.8 mmol/l, blood ketone 2.8 mmol/l, hydrogen ion concentration 47 mmol/l and serum bicarbonate 24 mmol/l. HbA1c was 96 mmol/mol and weight 106.2 kg with BMI 34.6 kg/m^2. Clinical signs of insulin resistance and hypercortisolaemia were observed; acanthosis nigricans, livid abdominal striae, proximal myopathy and gynaecomastia. Distribution of facial, axillary and pubic hair was normal and testicular volume was significantly reduced bilaterally (<5 ml). Total cholesterol was 5.4 mmol/l and LDL-C 3.5 mmol/l. Anterior pituitary profile confirmed 0900 testosterone 1.4 nmol/l, LH 13.1 U/l, FSH 23.3 U/l, TSH 1.89 mU/l, FT4 14.2 pmol/l and prolactin 1.74 mU/l. Cortisol adequately suppressed to <30 nmol/l after 1 mg dexamethasone. Glutamate decarboxylase (GAD) and islet antigen-2 (IA-2) antibodies were undetectable and c-peptide measureable (3.23 nmol/l [0.36−1.12]). Subcutaneous insulin was commenced with metformin (total daily dose 190 units). Karyotype was 47 XXY, in keeping with Klinefelter Syndrome. Bone densitometry is awaited and testosterone replacement therapy will commence after counseling.
Conclusion
The prevalence of metabolic syndrome in people with KS is 44%. The relative contribution of hypogonadism in the pathogenesis of diabetes remains unclear and both distribution and accumulation of adipose tissue may be more relevant. Testosterone replacement yields marginal cardiovascular benefit but has not been proven to attenuate diabetes risk. Acute hyperglycaemia is not a typical presenting feature of KS and current recommendations advise annual screening for T2DM following a positive diagnosis.

DOI: 10.1530/endoabs.65.P253

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St James's Hospital intensive care unit insulin discharge policy – A quality improvement project

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Background
Many patients require IV insulin during their critical illness. Maintenance of insulin in St James's Hospital ICU is governed by a local protocol. At the time of ICU discharge, IV insulin therapy is often stopped. Transitioning from IV to subcutaneous insulin is often done with endocrinology input. If this is unavailable inappropriate insulin dosing may increase the risk of hypo-/hyperglycaemia.
Aims
To reduce the number of episodes of hyperglycaemia (BG>14), hypoglycaemia (BG<4.0) and diabetic emergencies over the first 48 h following ICU discharge in patients requiring IV insulin.
Methods
All patients requiring IV insulin over the previous 6 months were highlighted using the ICU electronic patient record. Those on IV insulin on their day of discharge were isolated. Medical records were analysed to record episodes of hypo/hyperglycaemia that occurred in the first 48 h following discharge from ICU. A protocol for transitioning from IV to SC insulin was then developed and implemented. Rates of hypo/hyperglycaemia were then recorded in this group. Rates of each were compared.
Results
From November 2018 to April 2019 262 patients required IV insulin during their ICU admission. 56 were on IV insulin on their day of discharge. 19 were excluded due to inadequate data. 56.7% ($n=21$) were hyperglycaemic , 2.7% ($n=1$) had an episode of symptomatic hypoglycaemia and 8.1% ($n=3$) had hyperglycaemia with ketosis within 48 h after ICU discharge. From May to June 2019 14 patients underwent IV to SC insulin transition using our protocol. 1 was excluded as the protocol was not adhered to. 7.1% ($n=1$) were hyperglycaemic over the 48 h

following ICU discharge. There were no episodes of hypoglycaemia and no diabetic emergencies.
Discussion
This protocol appears to be safe and improves rates of hypo-/hyperglycaemia in a group of patients transitioning from a closed ICU to ward-based management.
DOI: 10.1530/endoabs.65.P254

P255

Ten years type 2 diabetes risks among doctors in Ondo State, South West Nigeria

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Background and objective
Diabetes mellitus is assuming worldwide increase with Doctors not being an exception. This study was carried out among Doctors in Ondo State South West Nigeria to assess 10 years risk of developing Diabetes using the Finish Diabetes Association assessment form.
Subjects, materials and method
This is a cross sectional study carried out in March 2019 at the Ordinary General Meeting. Two hundred and two (202) Doctors were screened after informed consent were obtained, using the Type 2 Risk Assessment Form by Finnish Diabetes Association. Anthropometric parameters, random blood glucose and BP were measured using standard protocols. Data was analyzed using SPSS 17. Level of significance was P value <0.05.
Results
Of the Two Hundred and Two Doctors screened, 55.9%(113) were males and 44.1%(89) females. Majority(63.4%) were below 45 years, 1.5%(3) above 64 years. 26.7%(54) and 11.4% (23) overweight and obese respectively. There were no gender difference in the level of obesity (P> 0.5). A quarter of the Doctors were not involved in adequate physical activity and 74.8%(151) do not eat vegetables or fruits everyday. 9.9%(20) were on medication for BP while 23.8%(48) were discovered to be hypertensives. 5%(10) had history of Diabetes and 5.9% (12) had elevated blood glucose. There was family history of DM in 24.3%(49) of the Doctors. The risks of developing DM was 32.2%),with 25.7% having slightly elevated risks, 2.5% (5) moderate, 2.5% high and 1.5% very high risks. There were no gender difference in the risk for developing DM P >0.5.
Conclusion
The 10 year risks of developing DM was high among the Doctors , majority were not taking adequate fruits and vegetables. More efforts need to be directed at regular screening and education of Doctors on lifestyle modification to reduce diabetes risks.
DOI: 10.1530/endoabs.65.P255

P256

Diabetic lipemia − acute pancreatitis and new diagnosis of diabetes

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Diabetic lipemia, remains a well recognized but rare manifestation of uncontrolled diabetes mellitus. Although prompt diagnosis and insulin treatment have probably reduced the incidence of hyperlipemia in symptomatic diabetes, reports of this poorly understood syndrome continue to appear. 48 year old male presented with a 2 day history of severe epigastric pain, radiating to his back. Associated symptoms included nausea with vomiting. Lethargic, tired and associated headaches. He was fit and well with no past medical history. Not taking any regular medications and no allergies. He was overweight, hypertensive with central abdominal pain radiating to his back. BM high. Initial blood results were inconclusive due to lipolysis. Venous blood appeared grossly lipemic. Triglyceride levels were high (result). Blood sugar elevated at 22. HbA1c was found to be at 161. Lipoclear, a solution which clears lipaemic serum, was applied to the venous blood. This allowed for the blood to be anlaysed and pancreatic enzymes (amylase and lipase) was checked. These came back as normal. USS abdomen was also reported as normal. Due to on-going epigastric pain a CT scan was done and this showed acute pancreatitis. The patient was started on IV insulin via the hyperglycaemia protocol. With improvements in blood sugar levels and treatment of his undiagnosed type 2 diabetes his triglyceride levels improved. Pancreatitis was treated with supportive measures and IV fluids. Pathophysiology is caused by abnormal metabolism of the triglyceride-rich lipoprotein associated with insulin deficiency, which reduces LPL activity and causes disturbed clearance of chylomicrons and VLDL from plasma. The surgical team were initially dismissive of the diagnosis of the pancreatitis due to the 'normal' pancreatic enzymes. It is however well documented that results following Lipoclear need to be interpreted with caution and due to the patients on-going pain a CT scan was able to confirm the diagnosis.
DOI: 10.1530/endoabs.65.P256

P257

Life threatening hypoglycaemia associated with illicit benzodiazepines

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A 53 year old male with a history of polysubstance abuse was admitted to A&E, having been found unconscious in the community with a blood glucose level of 1.2 mmol/l. Despite intramuscular glucagon and intravenous 20% dextrose administration, his blood glucose was confirmed to be 2.6 mmol/l on arrival in A&E. Neuroglycopaenia was refractory to multiple dextrose boluses and only stabilised following a continuous 20% 125 ml/hr dextrose infusion. Following admission to the High Dependency Unit the patient admitted 'street valium' usage, which was confirmed on urine toxicology. During a hypoglycaemic episode (2.3 mmol/l) concomitant C-peptide (5.43 nmol/l, range: 0.36−1.12) and insulin (81.4 mU/l, range: <13) levels were significantly elevated and β-hydroxybutyrate was supressed (0.1 mmol/l) suggestive of inappropriate endogenous hyperinsulinaemia. Urine sulphonylureas were negative. His response to a short synacthen test was appropriate, and abdominal imaging did not detect any lesions. Over the next 24−72 h the glucose infusion was weaned, and no further episodes of hypoglycaemia after 24 h were recorded either spontaneously or on fasting. No long-term sequelae have been demonstrated, however, this event would have resulted in significant morbidity or death if not recognised and treated appropriately. In Scotland there are 730 'drug-related deaths' per year and benzodiazepines are implicated in 59%. In our unit we have encountered a number of patients with severe hypoglycaemia and hyperinsulinaemia associated with illicit benzodiazepine use. These patients require continuous high concentration dextrose infusions and typically recover after 24−48 h. This case highlights the importance of blood glucose assessment in those with impaired conscious levels, regardless of suspected cause, and a potential mechanism by which illicit 'benzodiazepines' may result in drug-related deaths. Research is required to determine whether this effect is directly related to benzodiazepines or as a consequence of contamination.
DOI: 10.1530/endoabs.65.P257

P258

Severe peri-partum hyponatraemia: is oxytocin always the culprit?

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A 34-year old pregnant lady had induction of labour with prostaglandins and oxytocin infusion after her due date. She failed to progress in labour and became slightly disoriented. Urgent biochemistry revealed serum sodium of 124 mmol/l. She delivered a healthy baby by forceps but had post-partum haemorrhage of 1.5 l. Oxytocin infusion was continued along with Hartmann's solution. She became drowsy and biochemistry revealed serum sodium of 118 mmol/l, low serum osmolality, high urine osmolality and high urine sodium. Oxytocin infusion

was stopped and 0.9% normal saline commenced. She had diuresis of two litres over the next three hours. She clinically improved and serum sodium levels rose to 126 mmol/l. She admitted to drinking plenty of salt free fluids before delivery and had no symptoms and signs of Sheehan's syndrome or hypophysitis. Random cortisol was 620 nmol/l and thyroid function tests were normal. Serum levels normalised by the next day and her cognition returned to normal. This lady had dilutional hyponatraemia mainly caused by oral and IV fluids of low sodium content and was exacerbated by oxytocin infusion. Women tend to have asymptomatic low normal sodium due to dilution effect and inability to excrete free water in the later part of pregnancy. Oxytocin has activity on aquaporin receptors usually responsive to anti-diuretic hormone (ADH). Oxytocin administration is not an absolute contraindication and must be used with sodium containing solutions. An acute fall in serum sodium can not only lead to cerebral oedema but can also have serious implications for the baby including neonatal hyponatraemia. Hyponatraemia can be prevented with strict fluid monitoring, aiming to keep fluid balance as neutral as possible, serum sodium checks nearing labour and frequent sodium monitoring during labour. If sodium levels fall, close liaison with endocrinologists to consider oxytocin discontinuation and advice on fluid management is essential.

DOI: 10.1530/endoabs.65.P258

P259

Effectiveness of bariatric surgery – impact and metabolic outcome in different co-morbidities – a single center study in UK

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Introduction
Obesity is a global problem and its prevalence is on the rise in the U.K. It is associated with multiple co-morbidities with high mortality and has significant impact on healthcare costs. Bariatric surgery in recent past has revolutionized obesity treatment.
Aims
To assess effectiveness of bariatric surgery in terms of metabolic outcomes in patients with obesity in a single center in the UK.
Methods
Retrospective analysis of data was carried out from the medical records and laboratory database for all the patients with obesity who underwent bariatric surgery at Royal Berkshire Hospital from September 2016 until December 2017. Mean weight, BMI, HbA1C, Cholesterol, ALT, Vitamin B12, Folate and vitamin D levels were obtained at baseline pre-op and 1 year following surgery along with co-morbidities like diabetes, hypercholesterolemia, hypertension and sleep apnea.
Results
Patient data were collected from 120 patients (Mean Age 48.03 ± 9.59 years, Male 20.8%, Female 79.2%). 90% of surgeries were laparoscopic Roux-en-Y gastric bypass. Mean Follow up was 12.87 ± 2.65 months. Initial mean MDT weight was 135.77 ± 23.92 kgs which dropped to 124.37 ± 21.92 following induction into bariatric pathway to 90.11 ± 1.05 kgs post-operatively. Initial mean BMI reported as 48.36 ± 6.92 dropped to 32 ± 5.32 with post op EWL $68.46\% \pm 19.62$. HbA1c improved from baseline of 49.15 ± 17.52 to 35.42 ± 10.25 1 year post-operatively. Significant improvement with respect to all laboratory parameters and co-morbidities were observed post operatively with P-value < 0.05.
Conclusion
Bariatric surgery is an effective treatment for obesity and is associated with improvement of laboratory parameters and as a result, alleviation of metabolic syndrome. There is a need to educate people more regarding the effectiveness of the bariatric surgery.

DOI: 10.1530/endoabs.65.P259

P260

Diabetes-related knowledge, attitude and practice among patients attending a Tertiary Hospital in Kano, Northwestern Nigeria

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Introduction
Diabetes mellitus is the second non-communicable disease in Kano affecting 4.2% of the population.
Purpose/Specific aim
The aim is to assess the level of diabetes-related knowledge, attitude, and practice (KAP) among patients with diabetes in Kano. Also, the study sought to determine the relationship between the KAP and glycemic control.
Methods
This was a hospital-based cross-sectional study conducted at the diabetic clinic of MAWSH, Kano. A total of 400 participants that satisfied the inclusion criteria were recruited and their data analyzed. A KAP questionnaire modified from P and T journal media USA Inc was used to assess the KAP. Glycated hemoglobin was used to measure the level of glucose control of subjects.
Results
The mean age of the subjects was 51 years, and the majority of them are females (58.3%). Most of them have attained at least the secondary level of education. The mean knowledge score was 6.2 ± 3.1 points (out of 15), average attitude score was 2.5 ± 1.5 points (out of 5), and the mean practice score was 2.1 ± 1.3 points (out of 6). The mean total KAP was 10.7 ± 5.3 points (out of 25). The average glycated hemoglobin of the participants was 8.5 percent. The age of the participants, level of education, occupation, and average monthly income were found to be significantly associated with the KAP of the participants ($P < 0.05$). The level of KAP was found to be directly related to glycemic control ($\chi^2 = 63.9$ $P = 0.000$). The level of education (OR 5.0, 95%CI $0.196 - 0.452$, and monthly income (OR 4.4, 95% CI $0.123 - 0.326$) were found to be independent predictors of diabetes-related KAP.
Conclusion
The level of diabetes-related KAP was found to be low among diabetes patients in Kano, and this affects the management of the disease increasing the burden of managing non-communicable diseases in the community.

DOI: 10.1530/endoabs.65.P260

P261

Challenges in management of hypoglycemia presented post bariatric surgery

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A 39 years old lady who started to develop hypoglycemia three month following gastric bypass surgery. She is known to have Type 2 DM, dyslipidemia hypertension and Hirsutism. Her weight on presentation was 93.5 kg (pre operation was 104 kg) and Ha1c was 6% (pre operation was 10.5%). She was off diabetes medications. Hypoglycemia mainly fasting some readings < 3 mmol/l, with symptoms (diaphoresis, fatigue and weakness) but sometime hypoglycemia occur 2–3 h post prandial and also at night. She was started on Acarbose 25 mg three time daily (TID), Fibers enrichment of meals and continuous glucose monitoring inserted (CGM). Hypoglycemia persisted and we added Verapamil 120 mg and Acarbose increased to 50 mg TID. Two weeks later, because of recurrent hypoglycemia (glucose of 3.9 mmol/l), she was admitted. Her fasting insulin and C-peptide level were normal and Acarbose increased to100 mg TID. In Two weeks follow up her CGM revealed multiple hypoglycemic events, mostly asymptomatic and nocturnal & she admitted again. Her *Lab glucose was 2.76 mmol/l*, with concomitant inappropriately high Insulin level 8.4 mIU/l and detectable but not extremely elevated C-peptide 0.33 nmol/l. Normal adrenal response to ACTH stimulation and normal renal function. Urine screen for sulfonylureas screen and insulin AB were normal. We started Octreotide 50 mcg Q11 TID and continued on Acarbose & Verapamil. However, hypoglycemia persisted and Diazoxide 50 mg has been started and increased gradually. Her hypoglycemia improved and Acarbose and Octreotide stopped. Shortly following discharge, she re-presented with frequent hypoglycemic events on Diazoxide 150 mg, therefore, Octreotide was stated again. Pancreatic MRI was negative. Hypoglycemia, occurring after gastric bypass surgery, is challenging for patients and physicians . Acarbose and dietary modifications are the initial treatment and incomplete response need reassessment and father testing and additional pharmacological management.

DOI: 10.1530/endoabs.65.P261

P262

Audit on sodium glucose cotransporter-2 inhibitors (SGLT2) at Nottingham University Hospitals

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Aims/objectives
The aims of the audit were to assess if Sodium Glucose Cotransporter-2 inhibitors (SGLT2) were initiated in accordance with National institute of clinical excellence guidelines and appropriate effectiveness and reviews were performed in accordance with these guidelines.
Methods
A retrospective audit of 31 patients with Type 2 diabetes prescribed Sodium Glucose Cotransporter-2 inhibitors (SGLT2) between March 2014 and January 2017 at Nottingham University Hospitals was performed across both hospital sites in February 2017. The data was collected from the hospital software systems NOTIS and DIAMOND.
Results
The collected data showed patient's age range was between 26 and 83 years and duration of diabetes ranging from 4 years to 32 years. The audit demonstrated a significant reduction in HbA1C by 9.76 mmol per mol but no significant reduction in Blood Pressure or Body Mass Index after 6 months of therapy. The National Institute of clinical excellence targets for initiation (97%) and annual review (100%) of Sodium Glucose Cotransporter-2 Inhibitors (SGLT2) were achieved but the standards for documentation of the benefits and risks and continuation of therapy were not achieved.
Conclusions
The audit demonstrated that standards for initiation and annual reviews of the therapy were met but standards for documentation and continuation of therapy need improvement. We conclude that the significant optimisation of glycaemic control and osmotic symptoms despite a minimal reduction in Blood Pressure and Body Mass Index is promising enough to not preclude the use Sodium Glucose Cotransporter-2 inhibitors on further clinical reviews.

DOI: 10.1530/endoabs.65.P262

P263

BMI concordance in the United Arab Emirates (UAE): a study of 200 twin pairs

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Background and aims
We previously reported BMI heritability in the UAE to be 39.9%; indicating a high (60.1%) contribution of environmental factors to obesity. This study aims to determine and compare co-twin monozygotic (MZ) and dizygotic (DZ) BMI concordances.
Materials and methods
200 twin pairs were identified (ICLDC patient database) and split into two age groups ($\leq$18 and >18 years old). Opposite gender twin sets were considered DZ. In same gender twin sets zygosity was defined according to height differences between co-twins ($\geq$5 cm = DZ). BMI concordance was defined as a difference of $<3\ kg/m^2$. Concordance rates were calculated via pairwise concordance formulae then used to calculate the likelihood ratio (X^2) i.e. the significance of the difference between MZ and DZ concordance rates (critical value of 3.84 was based on 1 degree of freedom at a 0.05 statistical significance level).
Results
For children and adolescent twin sets ($n=96$, mean age 10.9 $\pm$ 4.1 years, BMI 18.9 $\pm$ 6.4 kg/m^2), (1) 64 pairs were concordant (MZ: 27 pairs)), (2) 32 pairs were discordant (MZ: 8 pairs)), (3) calculated pairwise concordance was MZ: 0.77 and DZ 0.61 and (4) X^2 for BMI concordance between MZ and DZ was 1.22. For the 104 adult twin sets: (mean age 46.8 $\pm$ 16.8 years, BMI 28.4 $\pm$ 6.7 kg/m^2), (1) 53 pairs were concordant (MZ: 28 pairs), (2) 51 pairs were discordant (MZ: 40 pairs), (3) calculated pairwise concordance was MZ: 0.41 and DZ: 0.69 and (4) X^2 for BMI concordance between MZ and DZ was 3.34.
Conclusion
Following null hypothesis X^2 model analysis, no association between zygosity and BMI concordance was indicated suggesting that environmental factors have a larger impact on BMI than genetics in this population.

DOI: 10.1530/endoabs.65.P263

P264

Dapsone-induced discordant glycated haemoglobin values in a patient with type 1 diabetes

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Introduction
Glycated haemoglobin (HbA1c) is used to measure glycaemic control in patients with diabetes, and accuracy depends on normal erythrocyte lifespan. Dapsone causes spuriously low HbA1c results by reducing erythrocyte lifespan through haemolysis and methaemoglobin formation, which interferes with the liquid-chromatography method used to measure HbA1c. Dapsone-induced haemolysis (DIH) is mostly reported in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, but there are rare reports in patients with normal G6PD who have high Dapsone levels during renal dysfunction or concomitant use of medications that use the cytochrome P-450 isoenzyme system. We report a case of DIH and spuriously low HbA1c values in a woman with diabetes.
Case
A 56-year-old female presented a record of low HbA1c values indicating excellent diabetes control despite raised random capillary blood glucose (CBG) levels indicating otherwise. She had type 1 diabetes on insulin treatment, coeliac disease and erythema elevatum diutinum for which she took Dapsone (50–100 mg daily) since 2013. HbA1c results were above 53 mmol/mol for several years indicating inadequate diabetes control but then dropped (<25 mmol/mol) while on Dapsone.
Investigation and management
Serum haematinics were normal. Reticulocyte count was high while in Dapsone (>81.0×10^9/l). Blood film demonstrated bite cells and red cell fragments suggestive of chronic low-grade DIH. Haemoglobinopathy and G6PD screens were normal. She had mild normocytic anaemia (110 g/l) with normal liver, thyroid and renal function. Simultaneous fructosamine and HbA1c values were 300 µmol/l and 19 mmol/mol, respectively (the estimated equivalent HbA1c value should be 50 mmol/mol). Therefore, CBG monitoring, subcutaneous sensors and fructosamine levels were used for monitoring diabetes control.
Conclusion
We have presented DIH and spuriously low HbA1c levels in a patient with diabetes that has normal G6PD levels and renal function. HbA1c monitoring in this group of patients is unreliable and other methods should be employed.

DOI: 10.1530/endoabs.65.P264

P265

Emphysematous pyelonephritis – medical management, a viable option

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Introduction
Emphysematous pyelonephritis(EPN) is a necrotizing infection of the renal parenchyma. Most cases occur in the setting of uncontrolled diabetes mellitus(DM). Presentation ranges from mild symptoms to shock and altered sensorium.
Objective
To highlight efficacy of intensive, appropriate medical therapy in management of a rare but life-threatening infection.
Case presentation
A 54-year old man presented with 3 week history of fever and left flank pain. A week earlier, he had developed cough and pleuritic chest pain. The patient was diagnosed with DM in current illness. On examination, he was acutely ill-looking, febrile(T38.9°C), dehydrated, with bilateral pedal oedema. He had tachycardia, tachypnea, coarse crepitation left lower lung zone, and left renal angle tenderness. Investigations: Random blood glucose 329 mg/dl, white blood count 26 026 cells/mm^3 with neutrophilia, anaemia (PCV26%), elevated ESR (112 mm/h) and azotaemia. Abdominopelvic CT scan showed multiple air densities in the left kidney, perinephric abscess, pleural effusion with passive atelectasis in left lower lung. Diagnosis was EPN (Class 3A) in Type 2 DM, complicated by pleural effusion and atelectasis. Intravenous fluids, antibiotics, insulin and supportive therapy were commenced. He made steady improvement in clinical and laboratory parameters; subsequently discharged to clinic.
Discussion
EPN is a potentially fatal bacterial infection. Gas accumulation in renal tissues suggests the diagnosis. It occurs mostly in uncontrolled, middle-aged, diabetic

patients, with a female preponderance. Surgical interventions ranging from drainage to nephrectomy have been considered choice treatment. As in index patient, however, intensive medical treatment yields favourable outcomes, reducing nephrectomy rates. Surgery should not be delayed in patients unresponsive to medical therapy.
Conclusion
Intensive medical therapy is a reasonable option in management of EPN. This limits frequency of nephrectomy in patients.

DOI: 10.1530/endoabs.65.P265

P266

Cushing's or not − a diagnostic dilemma

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We present the case of a 49 year old Caucasian lady who was referred for urgent evaluation to rule out Cushing's syndrome. She had progressive increase in bulk of her shoulders and upper arms over several months. She had a history of asthma, hypertension, and alcohol excess. She had inadvertently been using fostair (steroid inhaler) as a reliever up to 10 times a day. She denied anabolic steroid or drug use. She had no clinical features of Cushing's syndrome. There was no history of diabetes, osteoporosis or proximal myopathy.
Investigations
Investigations revealed low 24 h urinary cortisol of <25 nmol/24 h ($N= 30-145$ nmol/l), likely due to high dose inhaled steroids. Her short synacthan test, HbA1c and lipid profile was normal. Due to her unusual presentation, a diagnosis of partial lipodystrophy was considered and she was referred to Addenbrokes hospital for further tests. DXA measured the hypertrophied areas to be fat. She awaits results of genetic tests.
Discussion
The hypertrophy of upper trunk was due to symmetrical fat deposition confirmed on DXA test. A diagnosis of multiple symmetric lipomatosis (MSL or Madelung's disease) was made. Madelung's disease is a disorder of fat metabolism (lipid storage) that results in unusual fat accumulation around the neck and shoulder areas. The rest of the body may be lean in contrast to the affected parts. Peripheral neuropathy, diabetes mellitus, hypertension, and liver disease can be associated with MSL. MSL can rarely be associated with genetic mutation in MFN2 gene or a mitochondrial disorder. In our patient, MSL is likely due to alcohol excess. Genetic test results are awaited. We have advised her to limit alcohol use and inhaled steroid use to twice daily. If her symptoms are progressive, we will refer her to the plastic surgeons for consideration of liposuction.

DOI: 10.1530/endoabs.65.P266

P267

Social support and medication adherence among type 2 DM (T2DM) patients attending a public hospital in Lagos, Nigeria

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Background
Diabetes Mellitus is a chronic metabolic disorder with grievous complications affecting every aspect of patients' life. Availability of social support helps patients to cope better with the disease, hence positively affecting medication adherence and glycemic control.
Objectives
To assess the types of perceived social support and its relationship to medication adherence among T2DM patients attending a public hospital in Lagos, Nigeria.
Methodology
A cross-sectional study of 230 consenting adult T2DM patients selected by systematic random sampling and conducted at the General Hospital Odan, Lagos Island. An interviewer-administered questionnaire was used to gather information about the patients' socio-demographic and clinical characteristics. The Medical Outcome Study Social Support Survey and Morisky-8 item Medication Adherence Scale were used to obtain information about perceived social support and medication adherence respectively. Data were analyzed using the Statistical Package of Social Sciences version 20. Independent sample *t*-test was used to determine the difference in mean medication adherence between the two levels of social support and level of statistical significance was set at $P< 0.05$.
Results
Majority (57.8%) of the patients had a high level of social support. Tangible support was the highest form of social support available to the patients followed by affectionate support. About 43% of the patients had good medication adherence. Positive social interaction was the only type of social support that had a statistically significant relationship with medication adherence ($P= 0.031$).
Conclusion
Level of social support among our T2DM patients is high. Positive social interaction has a statistically significant relationship with medication adherence.
Keywords
T2DM, social support, medication adherence

DOI: 10.1530/endoabs.65.P267

P268

Social support and health-related quality of life among type 2 DM (T2DM) patients attending a public hospital in Lagos, Nigeria

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Background
Diabetes Mellitus is a chronic metabolic disorder with grievous complications affecting every aspect of the patients' life. Availability of social support helps patients to cope better with the disease, hence positively affecting their quality of life.
Objectives
To assess the level of perceived social support and its relationship to health-related quality of life of T2DM patients attending a public hospital in Lagos, Nigeria.
Methodology
A cross-sectional study of 230 consenting adult T2DM patients selected by systematic random sampling and conducted at the General Hospital Odan, Lagos Island. Data about the patients' socio-demographic and clinical characteristics were collected using an interviewer-administered questionnaire while those about perceived social support and quality of life were collected with the Medical Outcome Study Social Support Survey and WHOQOL-BREF questionnaires. Data were analyzed using the Statistical Package of Social Sciences version 20. Relationship between the domains of quality of life and types of social support was determined using the Spearman's correlation coefficient. Level of statistical significance was set at $P< 0.05$.
Results
Majority (57.8%) of the patients had a high level of social support, with the tangible support being the highest followed by affectionate support. All types of perceived social support (except positive social interaction) were positively and significantly correlated with all the domains of quality of life.
Conclusion
The level of social support among T2DM patients is high. Social support has a statistically significant relationship to health-related quality of life.
Keywords
T2DM, social support, quality of life

DOI: 10.1530/endoabs.65.P268

P269

Severe symptomatic hyponatraemia following a minor surgical procedure

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Introduction

Hyponatraemia following surgery is usually due to a mismatch between fluid input and output peri- and post-operatively. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is another important cause of hyponatraemia, commonest cause being medications, and intrathoracic and intracranial infections and neoplasia. SIADH has been reported to occur after pituitary surgery but rarely after other types of surgery. We present a severe case of SIADH-related hyponatraemia after minor surgery.

Case

A 70-year-old man presented to the emergency department complaining of vomiting, loss of appetite, fatigue, and abdominal discomfort. A week prior to presentation he had a transurethral resection of a bladder tumour, which was discovered during investigation for painless haematuria. He was asked to ensure adequate fluid intake post-surgery. He had a past medical history of type 2 diabetes for which he took Metformin and Simvastatin. His sodium level was normal prior to surgery. On examination his blood pressure was normal and he was clinical euvolaemic. Neurological examination was normal.

Investigations and management

Initial investigations revealed severe hyponatraemia (sodium 116 mmol/l), hypo-osmolality (234 mOsm/kg) and an inappropriately elevated urinary osmolality (577 mOsm/kg) and urine sodium level (74 mmol/l). His random cortisol rule out adrenal insufficiency and his thyroid and renal function test results were normal. He was diagnosed with acute SIADH. He was treated with concentrated sodium chloride solution (hypertonic saline) and oral fluid restriction. His serum sodium level was monitored which gradually improved over the next few days. He remains well.

Discussion

We have presented a case of SIADH with severe hyponatraemia following a minor surgical procedure. The condition may have been exacerbated by increased fluid intake post-operatively. Prompt treatment with hypertonic saline and controlled fluid intake is the mainstay of management while avoiding rapid correction of serum sodium levels which would precipitate pontine demyelination.

DOI: 10.1530/endoabs.65.P269

Neuroendocrinology

P270

Antisense oligonucleotides as a novel medical therapy for Cushing's disease

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Introduction

Cushing's disease (CD) is a rare but devastating condition, caused by hypersecretion of adrenocorticotropic hormone (ACTH) from a corticotroph adenoma in the anterior pituitary. CD is associated with a five-fold excess mortality and clinical features including hypertension, diabetes mellitus, osteoporosis, and depression. First-line treatment is transsphenoidal surgery, but this is effective in only 65% of cases and the relapse rate is high. Other treatment options are limited. Antisense therapy is a technique for inducing post-transcriptional gene silencing by the use of antisense oligonucleotides (ASOs), which target specific sequences on mRNAs leading to RNase-H degradation or steric blocking of ribosomal machinery. We hypothesised that ASOs against *POMC,* which encodes ACTH, could be an effective treatment for CD by silencing *POMC* expression and thus decreasing the secretion of ACTH.

Methodology

Two *POMC*-specific ASOs were used to transfect AtT-20 cells, which hyper-secrete ACTH. ASOs unrelated to *POMC* provided control data, and untreated cells gave baseline ACTH secretion. Modified ASOs contained a phosphorothioate backbone and 2'-*O*-methoxy nucleotides at the ends of the molecule. Changes in secreted ACTH levels in culture medium were measured by immunoassay, and were compared by ANOVA.

Results

ASOs specifically targeting *POMC* mRNA caused a sustained (up to five days) reduction (>65%) of ACTH secretion by AtT-20 cells compared to untreated cells (P values <0.05). ASO modifications resulted in a significant decrease in ACTH expression compared with the equivalent unmodified ASOs (P values <0.05). Control ASOs had no significant effect upon the secretion of ACTH.

Conclusions

ASOs targeting *POMC* mRNA reduced the secretion of ACTH by AtT-20 cells. Chemical modifications to the ASOs resulted in an increase in their efficacy. *POMC* ASOs could be a novel medical therapy for CD.

DOI: 10.1530/endoabs.65.P270

P271

Increased clot density in patients with acromegaly: the role of the adverse metabolic profile and disease activity to the increased thrombotic potential

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Introduction

Patients with acromegaly have increased mortality, primarily related to cardiovascular/cerebrovascular disease. The objective of this study was to evaluate whether GH/IGF-1 excess increases vascular disease by adversely affecting fibrin network characteristics.

Methods

In this case–control study, 40 patients with acromegaly (21 males, age 53 ± 13 years, 45% disease remission) and 40 age and gender-matched controls were recruited. Clot structure parameters were analysed using a validated turbidimetric assay and fibrin networks were visualised by laser scanning confocal microscopy (LSCM). Parameters of metabolic profile, body composition, plasma fibrinogen and PAI-1 were also assessed.

Results

Patients had higher BMI (30 ± 5.5 vs. 26.7 ± 4.1 kg/m^2, $P=0.003$), waist/hip ratio (0.91 ± 0.08 vs. 0.87 ± 0.08, $P=0.045$), total fat mass (29.8 ± 10 vs. 23.4 ± 10 kg, $P=0.003$), fibrinogen [3.1 (2.6–4.1) vs. 2.6 (2.5–2.7) mg/ml, $P<0.001$] and clot maximum absorbance (0.38 ± 0.13 vs. 0.32 ± 0.08 arbitrary units, $P=0.02$). There was a trend towards greater clot lysis area (measure of clot density, fibre thickness and lysis potential) in patients [634 (452–905) vs. 501 (429–784) arbitrary units, $P=0.08$], however there was no difference in lysis time or PAI-1 levels. LSCM showed increased fibrin network density in patients compared with controls, with increased number of fibrin fibres. Changes in clot density and fibrinogen were more pronounced amongst patients with active acromegaly and were eliminated when comparing patients in remission with controls. BMI, fat mass and skinfold thickness were associated with higher clot density and longer lysis time. Disease remission was associated with reduction in lysis area.

Conclusions

Patients with acromegaly have more compact clots secondary to higher fibrinogen levels, thus conferring increased thrombosis risk. The adverse metabolic profile and disease activity contribute to these abnormal clot structure properties. Prothormbotic fibrin networks may represent one mechanism for enhanced vascular risk in individuals with acromegaly, particularly during active disease.

DOI: 10.1530/endoabs.65.P271

P272

Developing a pyrosequenicng based assay for the detection of SDHC epimutations in clinical practice

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Background

The enzyme succinate dehydrogenase (SDH) functions in the citric acid cycle and loss of function of this enzyme can lead to the development of phaeochromocytoma/paraganglioma (PPGL), gastrointestinal stromal tumour (GIST) and renal

cell carcinoma. A germline mutation in one of the four genes (*SDH-A*/*B*/*C*/*D*) encoding the SDH complex is the most common mechanism of SDH inactivation causing SDH deficiency and is routinely screened for in clinical practice. SDH deficiency can also arise due to epigenetic silencing of the *SDHC* gene, but clinical testing for an *SDHC* epimutation is not widely available in the UK or Europe.
Objectives
I) To develop a pyrosequencing based assay for the detection of *SDHC* epimutations ii) to identify diagnostic pathways for the detection of an *SDHC* epimutation in clinical practice.
Design
SDHC promoter methylation analysis of 32 paraffin embedded tumours (including 17 GIST and 15 PPGL), matched normal tissue and germline DNA was performed using a pyrosequencing technique and correlated with *SDHC* gene expression.
Results
SDHC promoter methylation was identified in 18.7% (6 /32). All 6 cases had a presenting diagnosis of SDH deficient wtGIST and 3/6 cases had a multiple tumour syndrome including GIST, PPGL and pulmonary chondromas. *SDHC* hypermethylation correlated with reduced expression of the SDHC gene. No case of constitutional *SDHC* promoter hypermethylation was detected on analysis of germline DNA samples. Whole genome sequencing of germline DNA from three cases with a *SDHC* epimutation, did not identify any causative sequence anomalies to account for the focal hypermethylation in the *SDHC* promoter region in the tumours of these three cases.
Conclusion
This analysis has enabled us to recommend a diagnostic workflow for the detection of an *SDHC* epimutation in a service setting with the aim of improving the diagnosis, long term management and possible treatment options for patients with SDH deficient tumours in the future.

DOI: 10.1530/endoabs.65.P272

P273

Tissue responsiveness to cortisol: a novel clinical biosignature for the prediction of Nelson's syndrome

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Introduction
Nelson's syndrome is a significant long-term complication of bilateral adrenalectomy for Cushing's disease. However, evidence about possible factors that can predict its occurrence, is controversial and limited.
Objective
The objective of this analysis was to elucidate the role of various factors in prediction of Nelson's syndrome and the extent of their modifying effect.
Methods
All patients with Cushing's disease subjected to bilateral adrenalectomy ($n=45$) at a tertiary centre were recruited. Baseline clinical features, metabolic comorbidities, cortisol dynamics and IPSS in some patients were documented by retrospective data retrieval and prospective surveillance. MRI of the pituitary or GaDOTANOC/CT thorax and abdomen was done, for non-visualised adenoma. Nelson's syndrome was defined as an expanding (>2 mm) or newly appearing sellar adenoma with or without ACTH values exceeding 500 pg/ml.
Results
Nelson's syndrome had an incidence of 40% ($n=17$) on follow-up of 7 years with a median of 3 years for its development. All these subjects had a high ACTH(median 1004 pg/ml) except 2(ACTH <500 pg/ml). 9 subjects had an expanding and 8 had a *de-novo* sellar mass. Not all subjects with adenoma at baseline showed tumour progression ($n=12$), 2 of whom had received gamma knife prophylactically. TSS, done in 53% and gamma knife in the rest, were both curative. An annual increment in ACTH of 113 pg/ml/year (adjusted OR 26.36), uncontrolled hypertension (adjusted OR 16.91) and $\geq$ 4 discriminatory features of protein catabolism(adjusted OR 14.51) were predictive of Nelson's syndrome as were a significantly higher 1st year increment in ACTH (116 pg/ml) and 1st year absolute ACTH(142 pg/ml) (sensitivity and specificity exceeding 85%). The baseline ACTH and adrenal weight in these patients was lower($P>0.05$).
Conclusion
Nelson's syndrome can be predicted from the pre-operative presence of severe disease and post-operative higher rebound rise in ACTH.

DOI: 10.1530/endoabs.65.P273

P274

Heat shock protein profiling of Non-functioning pituitary adenomas

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Purpose
To identify predictive biomarkers of recurrence in NFPTs, we used heat shock protein profiling approach to correlate protein expression profiles with tumor recurrence. Heat shock proteins (HSPs) are synthesized by cells in response to various stress conditions, including carcinogenesis. The expression of HSPs in tumors has been implicated in the regulation of apoptosis. In the current study, we attempted to clarify the significance of HSPs in NFPTs and their correlation with clinicopathological parameters.
Experimental design
Expression levels of the HSP27, HSP27pS15, HSP27pS82, HSP47, HSP60, and HSP70, were studied using immunohistochemistry on 200 NFPTs. Normal pituitaries from 10 healthy patients were used as controls in the study. Among 200 h NFPTs, 44 patients have a recurrence after undergoing primary resection. HSP expression was evaluated according to the percentage of positively stained cells, and the intensity of staining. Data are presented as the mean $\pm$standard deviation of the mean (S.D.). *P*-value <0.05 was considered as significant.
Results
Patients were in the age group of 28–65 years, with a mean age of 43.1 ($\pm$12.6) years. Immunohistochemistry with SF-1 and FSH/LH-α classified 45.5% NFPT as gonadotropinoma 3% silent somatropinoma (pit-1 positive), and 7.5% silent corticotropinoma (T-pit positive). Among these 200 patients, 44 recurrence events were observed after a total of 15 years of follow-up (median$=4$ years). Among all the HSPs, HSP47, HSP60, and HSP70 were under-expressed while HSP27pS82 was augmented ($P<0.001$) in recurrent tumors. HSP27pS82 was also overexpressed in invasive NFPTs ($P=0.01$). There was no change in HSP27 and HSP27pS15 expression levels. ROC curve indicated HSP27pS82 as a good marker for discriminating recurrent tumors from non-recurrent tumors (AUC $=$ 0.738).
Conclusions
Thus, we conclude that HSP27pS82 could be a good prognostic marker for recurrent NFPTs. Additionally, HSP27pS82 can also serve as a therapeutic target.

DOI: 10.1530/endoabs.65.P274

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Predictive power of ACTH and cortisol in the early post-operative period following pituitary surgery: relationship to long term glucocorticoid requirement

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Hypothalamic–pituitary–adrenal (HPA) axis function after trans-sphenoidal pituitary surgery is commonly assessed using post-operative morning cortisol. We performed a prospective study to determine the sensitivity and specificity of cortisol and ACTH measured within the first 24 h, in predicting glucocorticoid requirement at 6 months both in patients with pre-operative secondary adrenal insufficiency (SAI) and with normal pituitary function. Exclusion criteria included exogenous supraphysiological glucocorticoids, pregnancy and Cushing's disease. ACTH and cortisol were measured at $+4$ h and $+8$ h after induction of anaesthesia on Day 0 and every 10 min between 0700 h and 0900 h on Day 1.
Results
Five of 19 participants had pre-operative SAI, of which 3 recovered post-operatively. One participant with normal HPA function pre-operatively developed symptomatic diabetes insipidus and SAI after Day 1. At 6 months, 3 participants required glucocorticoids (SAI) and 16 did not (normal HPA axis). ACTH on Day 0 at $+4$ h $\geq$65 ng/l predicted a normal HPA axis at 6 months (AUC:0.844, $P=0.004$, sensitivity:100%, specificity:75%), but not $+8$ h levels ($P=0.697$). Serial cortisol measured between 0700 h–0900 h showed median difference between peak and trough concentrations of 172 nmol/l (IQR 121–198). Day 1 ultradian cortisol peaks occurred at 0710 h and 0840 h and cortisol levels of $\geq$445 nmol/l (AUC:0.844, $P=0.04$, sensitivity:100%, specificity:69%) and $\geq$307 nmol/l (AUC:0.9, $P<0.001$, sensitivity:100%, specificity:80%) respectively, predicted normal HPA axis at 6 months. Combining Day 0 $+4$ h ACTH and Day 1 cortisol levels referenced to these peaks increased the specificity to

87.5% and 100%, respectively, whilst maintaining 100% sensitivity. Three Day 1 morning cortisol levels taken 30 min apart between 0700 and 0900 h, increased the probability of sampling an ultradian peak within 10 min to 100%.
Conclusion
Immediate post-operative +4 h ACTH and three Day 1 morning cortisol samples 30 min apart between 0700 and 0900 h predict a normal HPA axis at 6 months. Patients with new onset symptomatic SAI or pituitary dysfunction require further testing.

DOI: 10.1530/endoabs.65.P275

P276

The effect of tumor staining pattern on secondary hormonal deficiency in nonfunctioning pituitary adenomas

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Secondary hormonal deficiency (SHD) is common in patients presenting with nonfunctioning pituitary adenomas (NFA). NFA can either stain for various hormones or be non-hormone staining on immunocytochemistry. To date, no study has assessed the association between staining pattern of NFA and pattern of SHD at presentation. The Halifax Neuropituitary Program has been prospectively collecting comprehensive data on all neuropituitary patients in the province of Nova Scotia, Canada since November 2005. For this study, we conducted a retrospective analysis of 167 consecutive patients with NFA who had undergone surgery in our centre and reviewed their pathology data including immunocytochemistry as well as hormonal profile at presentation. Of those, 72 (43.1%) did not stain for any pituitary hormone, 66 (39.5%) stained for a single hormone and 29 (17.4%) stained for multiple hormones. Of the single staining NFA, follicle stimulating hormone staining was the commonest, accounting for 28 (16.8%) of cases. A logistic regression analysis was conducted to identify any association between stating pattern and SHD correcting for age, gender and size of tumour at presentation. Our data showed that NFA which stained for multiple hormones were significantly less likely to cause SHD (OR = 0.26, CI 0.1–0.7; $P < 0.001$) whereas there was no difference in SHD patterns in NFA with single vs. no hormone staining (OR = 0.98, CI 0.43–2.24; $P = 0.96$). These novel data suggest that staining pattern in NFA is associated with SHD and raise the possibility of additional autocrine/paracrine factors that may cause SHD in these patients.

DOI: 10.1530/endoabs.65.P276

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Secondary hormonal deficiency patterns vary among different types of sellar masses despite similar size at presentation

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Secondary hormonal deficiency (SHD) in sellar masses (SM) is thought to be partly due to compression of the portal vessels by the enlarging tumour restricting the blood supply to the normal pituitary tissue. However, to date no study has looked at the patterns of SHD in various types of SM and assessed if SHD is related solely to the size of SM or is associated with the underlying pathology. We assessed 914 patients with SM enrolled in our comprehensive pituitary registry since November 2005 and analyzed the pattern of SHD at presentation in relation to tumour type and size at presentation. While there was an overall trend of a higher rate of SHD in larger SM ($P < 0.0001$), the rates of SHD were significantly different in various types of SM despite similar size. The rates of SHD in SM < 9 mm were: Nonfunctioning adenoma [NFA] (10%), Prolactinoma (49%), GH adenoma (13%), ACTH adenoma (33%), craniophaygioma (50%), meningioma (0%) and Rathke's cleft cyst [RCC] (11%); 10–19 mm were: NFA (35%), Prolactinoma (73%), ACTH adenoma (30%), GH adenoma (23%), craniopharyngioma (48%), meningioma (5%) and RCC (17%); 20–29 mm were: NFA (64%), Prolactinoma (78%), ACTH adenoma (100%), GH adenoma (75%), meningioma (16%), craniopharyngioma (70%) and RCC (41%) and > 30 mm were: NFA (83%), Prolactinoma (100%), GH adenoma (80%), meningioma (27%) and craniopharyngioma (88%) (all $P < 0.001$). Furthermore, of the two largest categories of SM, NFA have higher odds ratio (3.34; CI = 1.89–5.89) of presenting with multiple SHD when compared to prolactinomas, despite similarity in gender, age and size of the tumour ($P < 0.001$). These novel data suggest that SHD patterns vary among different types of SM and are not solely dependent on tumour size. Our data also show that NFA are more likely to present with multiple hormonal deficiencies.

DOI: 10.1530/endoabs.65.P277

P278

Distinct methylation patterns in sparsely and densely granulated growth hormone-secreting pituitary tumours provide clues to different underlying tumorigenic mechanisms

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Objectives
Somatotropinomas can be divided into three subgroups based on their distinct DNA methylation profiles[1], one matching sparsely granulated (SG) and the other two matching densely granulated phenotypes (DG-A and DG-B). Sparsely granulated adenomas show fibrous body formation on cytokeratin immunohistochemistry, compared to diffuse staining in densely granulated adenomas. Methylation[1] and gene expression data were analysed to identify (i) differentially methylated regions (DMRs) and genes between SG, DG-A and DG-B and normal pituitary (NP), and (ii) genes showing differential promoter methylation with differential expression.
Methods
We identified.

- DMRs using bumphunter (minimum probes/ DMR = 7, adjusted $P < 0.05$),
- differentially expressed genes from Affymetrix data (false discovery rate < 0.05, fold change of ≥ 2),
- gene sets using gene set enrichment analysis (Fisher's exact test ($P < 0.05$)),
- interaction hotspots using EpiMod ($P < 0.05$).

Results
All tumour subgroups showed predominant hypomethylation compared to normal, with striking profound hypomethylation observed in DG-B. Three genes showed promoter hypermethylation with decreased RNA expression, including *IER3* (SG vs.NP), with a known pro-apoptotic role in cervical cancer. Twenty-one genes showed promoter hypomethylation with increased RNA expression, including *TET1* (DG-B vs. NP), which is a demethylating agent and may cause the profound hypomethylation in DG-B tumours. *ITPR2* and *SFRP1* showed promoter hypermethylation with decreased expression in SG vs. DG-B tumours. *ITPR2* mediates oncogene-induced senescence and *SFRP*1 inhibits Wnt signalling, both consistent with tumour suppressive roles. Subnetworks based around inflammatory mediators show predominant promoter hypo-methylation (DG-B vs. DG-A/ DG-B vsSG), suggesting a key role for inflammatory mediators in DG-B tumours.
Conclusions
Pathways involving apoptosis, demethylation and inflammation mediate different tumorigenic pathways in pituitary adenomas with different cytokeratin-staining patterns on immunohistochemistry.
Reference
1. Capper, D. *et al.* DNA methylation-based classification of central nervous system tumours. *Nature* **555**, 469–474, doi:10.1038/nature26000 (2018).

DOI: 10.1530/endoabs.65.P278

P279

CACNA1C genotype does influence CACNA1C methylation and the association with cortisol release/potential mental health resilience

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Introduction
CACNA1C gene encodes the L-type voltage dependent calcium channels and its variants are associated with susceptibility to psychiatric disorders. We recently provided evidence of a genotype-by-environment interaction of the *CACNA1C* rs1006737 polymorphism, suggesting that the cortisol awakening response (CAR), an indicator of HPA-axis function, might be increased in non-risk allele carriers (GG) who have experienced childhood trauma (CT). In these individuals a heightened CAR may be indicative of mental health resilience. We subsequently investigated if epigenetic changes could modulate the genotype-conferred resilience in relation to reported CT.
Methods
Genomic DNA was extracted from saliva ($n=114$, male). We analysed 11 CpGs of *CACNA1C* gene, previously investigated in the context of suicide attempt. 2×2 ANCOVAs with CACNA1C genotype (AA/AG or GG) and CT (yes/no) as main factors and age as a covariate were conducted. In addition, the relation between the methylation levels and the CAR, current perceived stress (PSS-14) and depression (HADS) were investigated using multiple linear regression.
Results
No significant differences between the *CACNA1C* gene rs1006737 AA/AG and GG groups in terms of age, years of education, current perceived stress (PSS-14) and depression (HADS) ($P>0.05$) were found. Individuals homozygous for the non-risk allele (GG) showed decreased methylation levels at CpGs 3, 4 and 7. GG genotype individuals who experienced CT showed lower methylation across most of the CpG sites. Conversely, risk allele A carriers had increased methylation levels in comparison to non-risk homozygotes (GG). Regression analysis revealed that lower methylation at CpG2 ($B=-0.270$, $P=0.043$) and CpG 3 ($B=-2.75$, $P=0.041$) was associated with a greater CAR (subset $n=66$).
Conclusion
The findings suggest there may be a relation between decreasing *CACNA1C* methylation and increased CAR, a measure of psychological resilience. This could be a mechanism for conferring resilience and healthy adaptation to the trauma experience in these individuals.

DOI: 10.1530/endoabs.65.P279

P280

Prognostic indicators of metastatic neuroendocrine tumour of unknown primary site: a single centre retrospective study

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Neuroendocrine tumours (NETs) presenting as metastatic cancer of unknown primary site (CUP) are suspected to confer poorer prognosis compared to metastatic NETs of known primary site. We performed a retrospective, single centre study to determine the prognostic indicators in CUP-NETs compared to metastatic small intestinal NET (SiNET), before and after adjusting for factors known to affect overall survival. Subjects were selected from a departmental database of 1050 NET patients discussed by the Oxford neuroendocrine service between 2011 and 2019. Inclusion criteria were histologically proven NET with radiological evidence of metastatic disease at diagnosis. Survival time began from the date of histological diagnosis until the last known follow-up. The primary endpoint was death. Patients were divided into 3 cohorts: 1) CUP-NET, no primary identified; 2) likely SiNET, radiological evidence of mesenteric/SiNET, and 3) histologically confirmed SiNET. Cox proportional hazards models were constructed to compare unadjusted and adjusted hazard ratios (HR) for age, tumour differentiation [well vs. poor], grade and primary tumour resection [likely SiNET and SiNET] between each group: 233/1050 (21%) patients with metastatic NET (median follow-up of 22.5 months [95% CI 16−29, IQR 9−55]) were identified including 52/1050 (5%) CUP-NET, 66/1050 (6%) likely SiNET and 105/1050 (10%) SiNET. Unadjusted mean (standard error) overall survival data were 19 (2.4), 64 (5.8) and 102 (5.6) months respectively ($P<0.02$). Table 1 reports the unadjusted and adjusted HR for overall survival between each group. In conclusion, CUP-NET confers a poorer prognosis compared to metastatic SiNET. However, this difference is largely driven by patient age, tumour grade and differentiation.

Table 1 Unadjusted and adjusted hazard ratios (HR) for all cause mortality

Groups	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
CUP-NET to likely SiNET	3.1 (1.5−6.3)	0.8 (0.3−2.1)
CUP-NET to SiNET	6.5 (3.3−13.0)	1.8 (0.6−5.6)
Likely SiNET to SiNET	2.5 (1.4−5.7)	1.6 (0.2−13.8)

DOI: 10.1530/endoabs.65.P280

P281

Clinical PhenClinical phenotypes of GNAS gene mutations in Korean Acromegalic Patientsotypes of GNAS gene mutations in Korean acromegalic patients

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Background
Guanine nucleotide-binding protein, α stimulating (GNAS) gene have been reported to be associated with GH secreting pituitary adenoma. Approximately 40% of patients with acromegaly have GNAS mutation. In this study, we investigated the prevalence of GNAS mutation in Korean acromegalic patients and assessed the correlation with the biochemical or clinical characteristics.
Method
We studied acromegalic patients who underwent surgery between from July 2005 to January 2017 in Severance Hospital. GNAS gene analysis was performed with amplications of regions containing hotspot 2 sites of activating somatic mutations in codons 201 and 227. We evaluated the age, gender, GH, IGF-1 levels, postoperative biochemical remissions and immunohistochemical staining results of tumor.
Result
GNAS mutations were present in 75 of the 126 acromegalic pateints (59.5%). Among the GNAS mutant patient, 61 subjects (81%) had mutation in codon 201. There was no difference in age distribution and Hardy classification according to GNAS mutation. Female proportion was 76.5% and 48.0% in GNAS wild type and mutant group, respectively ($P=0.006$). GNAS mutant group had higher prevalence of overall GH expression in immunohistochemical staining (98.7% vs. 92.2%, $P = 0.015$). Furthermore, they had higher IGF-1 level preoperatively (791.3 vs. 697.0 ng/ml, $P=0.045$). Immediate postoperative nadir GH (0.3 vs. 0.6 ng/ml, $P=0.012$) in oral glucose tolerance test (OGTT) was lower in GNAS mutant patients. Surgical remission rates were significantly higher in GNAS mutant patients, evaluated both at immediately and at 6 months after operation (70.7% vs. 54.9%, $P=0.011$; 85.3% vs. 82.4%, $P=0.007$, respectively).
Conclusion
In conclusion, GNAS mutation was more frequently found in Korean acromegalic patients. GNAS mutation positive tumors tended to have higher preoperative IGF-1 level, surgical remission rate and lower immediate postoperative nadir GH on OGTT. Identifying the GNAS mutation would be helpful in predicting patient's clinical features and prognosis.

DOI: 10.1530/endoabs.65.P281

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Onset of radiation-induced hypopituitarism in pituitary adenomas

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Introduction
Radiotherapy (RT) can achieve tumour control rates of over 90% in patients with pituitary adenomas. The commonest toxicity of irradiation is hypopituitarism.

The exact incidence is variable and requires long-term intermittent testing for deficiency of all hypothalamic−pituitary axes (HPA). The aim of this study is to determine the time to onset of individual hormonal deficiencies and establish a time frame for endocrine testing during follow-up post-RT.
Methods
We retrospectively assessed the late effects of irradiation on pituitary function in patients with pituitary adenomas treated over 2004−2015. Patients with acromegaly or Cushing's disease, those with tumour recurrence undergoing surgery after radiotherapy and patients with incomplete endocrine data during follow-up were excluded.
Results
94 patients (59% male; age at RT 58.4±12.3 years) were included. Mean duration of endocrine follow-up post-RT was 7.6±3.1 (range: 1.3−14.3) years. 90.4% of patients ($n=85$) received external beam radiotherapy. Thirty patients (31.9%) had complete loss of anterior pituitary hormone function pre-RT. Overall prevalence of radiation-induced hypopituitarism was 65.6%. The incidence and mean time to onset of individual hormone deficits post-RT were: GH–57.1% (8/14, 1.3±0.7 years); LH/FSH–50% (11/22, 2.0±1.4 years); ACTH–43.3% (26/60, 3.1±2.2 years, $P=0.04$); TSH–39.6% (19/48, 2.9±1.7 years, $P=0.01$). Age at RT, gender, dose of RT and severity of hypopituitarism pre-RT did not correlate with post-RT hypopituitarism. By 5 years 100% GH, 75% LH/FSH, 60% ACTH and 75% TSH deficiencies were evident. All HPA dysfunction were detected by 8 years.
Conclusion
A gradual increase in the prevalence of all anterior pituitary hormone deficits was observed. GH axis was the most radiosensitive and ACTH deficiency was of slowest onset. Regular testing is mandatory for at least 8 years to ensure timely diagnosis and early hormone replacement therapy.
DOI: 10.1530/endoabs.65.P282

P283

Review of acromegaly management and outcomes in Imperial College Healthcare NHS Trust over eleven years
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Background
Acromegaly is associated with multiple co-morbidities and increased mortality. Surgery is the first-line intervention and remission of acromegaly can restore normal life-expectancy. Pre-operative somatostatin analogues (SSA) may increase the likelihood of remission in large invasive tumours by causing tumour shrinkage prior to surgery.
Aims
To audit the management of acromegaly patients at Imperial College Healthcare NHS Trust (ICHNT) against the 2018 consensus statement on acromegaly therapeutic outcomes and subsequent remission rates compared to recently published meta-analyses.
Methods
All patients diagnosed with acromegaly from 2008 to 2019 at ICHNT were identified. Electronic patient records were reviewed for biochemical data at diagnosis and post-surgery. Early remission, defined as an age- and gender-normalised IGF-1 and random growth hormone <1 mcg/l, was assessed 3−6 months post-operatively. Patients were categorised as presenting with micro-adenomas (Mic), or macroadenomas with cavernous sinus invasion (MacI) or without invasion (MacNI). Administration of pre-operative SSA was recorded.
Results
Seventy-five patients with acromegaly were identified (Mic $n=12$; MacNI $n=42$; MacI $n=21$). Ninety-one percent ($n=68/75$) underwent endoscopic trans-sphenoidal pituitary surgery as their primary intervention, 5% ($n=4/75$) received primary medical therapy, 3% ($n=2/75$) primary radiotherapy, 1% ($n=1/75$) no intervention. Twenty-six percent ($n=18/68$) of surgical patients received pre-operative SSA, but remission rates were similar to those who did not (50% vs. 49%, $P=0.94$). Post-operative remission rates were 67% ($n=6/9$) for Mic, 68% for MacNI ($n=27/40$), but only 5% ($n=1/20$) for MacI.
Conclusions
Remission rates following surgery at ICHNT were comparable to previously reported rates of 67−83% for Mic and 63.3−76.3% for MacNI. Lower remission rates (41%) have been reported for MacI, and cavernous sinus invasion has been reported to negatively correlate with remission. Our low MacI remission rate (5%) may be due to the inclusion of debulking surgeries where remission would not have been expected. Pre-operative SSA treatment did not alter the biochemical remission rate.
DOI: 10.1530/endoabs.65.P283

P284

Silent somatotroph pituitary neuroendocrine tumours (PitNETs): systematic review of cases from a Pituitary Centre
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Introduction
Silent somatotroph Pituitary Neuroendocrine Tumours (PitNETs) are extremely rare (2−3% of surgically treated pituitary tumours) and data on their natural history and outcomes are scarce.
Aim
To review systematically the cases of these tumours presenting in our Centre.
Patients and methods
Patients with this diagnosis were identified from our Pituitary Registry and clinical/laboratory/imaging data were collected and analysed.
Results
Sixteen cases were identified [10 females−6 males, median age at diagnosis: 52 years (26−64)]. Two patients presented with apoplexy (13%), whereas in two, the tumour was found incidentally (13%). Visual field defects were detected in 69% of cases with available data. All tumours were macroadenomas; supra/para/infrasellar extension was present in 81%, 56% and 38%, respectively. Surgery was performed by transsphenoidal approach in 94% of cases and adjuvant radiotherapy was offered in three patients (19%) (45 Gy in 20 or 30 fractions). In all, except one case, there was partial tumour removal. During median follow-up of 12.1 years (0.25−26), seven patients had tumour regrowth (46.7% − one excluded due to short follow-up) at a median interval of 3.1 years (2.6−10.3) since surgery [50% of those treated solely by surgery (regrowth probability 55.6% at 5-years and 10-years) and 33.3% of those treated by surgery + radiotherapy]. Regrowths were managed by surgery ($n=3$), radiotherapy ($n=1$), surgery + radiotherapy ($n=1$) and observation ($n=2$) . Two patients had second growth. None of the patients developed clinical acromegaly during follow-up.
Discussion/conclusions
In our series, the majority of silent somatotroph PitNETs had supra/parasellar extension. In comparison with historical data and within the constraints of our small sample size, the 10-years regrowth probability of those treated solely by surgery fall within the reported range for non-functioning PitNETs. Larger scale studies aiming to clarify whether this tumour subtype is characterised by aggressive clinical behaviour are needed.
DOI: 10.1530/endoabs.65.P284

P285

The argument for growth hormone day curve testing in acromegaly; significant discrepancy between mean growth hormone and random growth hormone levels
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Endocrine Society guidelines recommend random growth hormone (RGH) < 1 mcg/l as indicative of biochemical control of acromegaly. Growth hormone (GH) control may also be determined using the mean GH (MGH) of a growth hormone day curve (GHDC). We report a retrospective analysis of 461 consecutive GHDCs, from 121 patients with treated acromegaly, performed in a single centre between 2009 and 2019. Each GHDC contained 7–9 GH measurements (mean 8.9) taken at regular intervals over 9-hours. Each individual GH measurement was treated as a RGH ($n=4113$) and compared against the MGH of its own curve. Contemporaneous IGF1 levels, expressed as a fraction of the sex- and age-adjusted upper limit of normal, were recorded. GH was measured on a Siemens Immulite 2000 assay. IGF-1 was measured on the Immulite 2000 assay prior to 2013, and subsequently on an IDS iSys assay. Sequential RGH levels displayed significant variance (mean $\pm$ SD; 0.57 ± 2.64). Variance was greater if MGH ≥ 1 mcg/l (1.12 ± 3.88) compared to MGH < 1 mcg/l (0.13 ± 0.27, $P=0.00005$). Disagreement (defined as either RGH < 1 mcg/l and MGH ≥ 1 mcg/l, or RGH ≥ 1 mcg/l and MGH < 1 mcg/l) was observed in 191/461 (41.4%) GHDCs, involving 510/4113 (12.4%) RGHs. 271/4113 (6.6%) RGHs significantly underestimated MGH, with 75/4113 (1.8%) of RGHs < 1 mcg/l despite corresponding MGH ≥ 1.5 mcg/l. RGH ≤ 0.3 mcg/l had a predictive value of 94.9% (444/468) for MGH < 1 mcg/l. 204/4113 (5.0%) RGHs significantly overestimated MGH, with 70/4113 (1.7%) of RGHs ≥ 1.5 mcg/l despite corresponding MGH < 1 mcg/l. RGH ≥ 2 mcg/l had a predictive value of 96.2% (842/875) for MGH ≥ 1 mcg/l. Rates of GH discordance (GH ≥ 1 mcg/l, IGF1 $\leq$ULN) and IGF1 discordance (IGF1 >ULN, GH < 1 mcg/l) were similar for RGH (644/4113, 15.6% and 733/4113, 17.8%) and MGH (70/461, 15.2%, $P=0.1367$ and 82/461, 17.8%, $P=0.986$). We conclude that RGH displays significant variance, is frequently (12.4%) in disagreement with MGH, and often significantly overestimates (5.0%) or underestimates (6.6%) GH exposure.

DOI: 10.1530/endoabs.65.P285

P286

Efficacy and safety of Temozolamide therapy as a part of multimodality treatment in patients with pituitary adenomas: experience from a single pituitary centre of excellence

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Objective
To study O6-methylguanine-DNA methyltransferase (MGMT) immunoexpression to access the efficacy of Temozolamide (TMZ) as a part of multimodality treatment.
Background
Aggressive or residual pituitary tumours are associated with substantial morbidity. Treatment options are often limited, and chemotherapy are associated with dismal results. Recent reports have documented the efficacy of TMZ therapy in aggressive pituitary tumors resistant to multimodality therapy. A DNA repair protein, MGMT has been suggested as a biomarker to predict response to TMZ in pituitary tumours.
Design
A total of 28 patients on TMZ therapy on conventional cycles (5/28 days, first cycle-150 mg/m^2, subsequent cycles-200 mg/m^2, at least three cycles) were analysed. Immunohistochemistry for MGMT could be performed on 20/22 patients who underwent surgery. In addition to MGMT, tissues were also examined for Ki-67 and p53. Relevant positive and negative controls were used for validation. Statistical analysis was done using GraphPad PRISM 7.0. Response was defined according to RECIST criteria for imaging and hormonal values.
Results
There were 14 somatotropinomas (one microadenoma, one primary Gamma Knife Radiosurgery (GKRS)), 12 Prolactinomas (5 not operated, received D2 agonist followed by TMZ as add on), and 2 NFPTs. All patients responded to TMZ therapy (complete3/partial14/stable disease 11). There was significant decrease in prolactin ($P=0.004$) and IGF-1($P=0.006$) in prolactinomas and somatotropinomas respectively. We also observed significant reduction in tumor volume ($P<0.0001$). Patients who received TMZ post gamma knife surgery responded better ($P=0.02$) as compared to post intensity modulated radiotherapy. ($P=0.16$). Apoplexy, Knosp grading, number of surgeries, Ki-67, p53 were not predictive of response to TMZ therapy. A significant proportion of pituitary adenomas demonstrate low MGMT immunoexpression (10/16), however, responders had differential expression of MGMT ($P<0.001$).
Conclusion
Contradictory to popular belief MGMT expression on IHC can still be used for predictor of response to TMZ therapy in real world setting.

DOI: 10.1530/endoabs.65.P286

P287

Cannulated prolactin as a diagnostic tool for true hyperprolactinaemia

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Background
Hyperprolactinaemia is the common endocrine disorders. More commonly diagnosed in women due to menstrual irregularity, infertility and galactorrhoea. Hyperprolactinaemia can be due to many physiological stimuli such as stress, sleep, exercise, medications, primary hypothyroidism, renal failure, chest wall lesion. Stress of venepuncture can contribute to hyperprolactinaemia as well.
Patient and methods
We conducted a retrospective analysis of the 46 patients those have undergone cannulated prolactin between 2018 and 2019. The information was gathered by reviewing the clinic letters, biochemical and radiological results electronically. We reviewed the past medical history, Pituitary MRI results. A cannula was inserted in the ante-cubital fossa and immediately a prolactin sample was drawn. Repeat prolactin was measured after 20 and 40 min.
Results
The data involved 40 (87%) female and 6 male. Mean age of the patients was 32.41 years. Mean referral prolactin was 920 Mu/l (SD. 408). 27 (57%) had normal prolactin value after cannulation. Of these 27 patients 12 (44%) had Pituitary MRI that was normal in majority with 2 incidental microadenoma and one Ratke's cleft cyst.
Conclusion
Cannulated prolactin to be considered whilst dealing with asymptomatic hyperprolactinaemia with a prolactin value of <2000 Mu/l. This will avoid the unnecessary investigations.

DOI: 10.1530/endoabs.65.P287

P288

Modalities to overcome resistance to dopamine agonists in patients with macroprolactinomas

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Background
Dopamine agonists (DA) are the first-line treatment for macroprolactinomas. However, up to 10% of patients fail to respond to medical therapy.
Aim
To assess biochemical resistance rate to DA treatment in a large series of patients with macroprolactinoma and to analyze possibilities to overcome this resistance.
Patients and methods
195 patients with macroprolactinomas, treated with DA for at least 2 years, were retrospectively reviewed. Serum prolactin levels were measured by chemiluminescence. Tumor dimensions were assessed by computed tomography scan or MRI. Biochemical resistance to DA therapy was defined as failure to achieve normoprolactinemia on DA high dose (Bromocriptine 30 mg/day or Cabergoline up to 3.5 mg/week).
Results
16 patients (8.2%) resistant to DA were identified: 8 men and 8 women, aged 30.8 $\pm$ 16.5 years at diagnosis; median prolactin at diagnosis was 1516.8 ng/ml and average tumor diameter was 3.2 $\pm$ 1.6 cm (range: 1−6.8 cm); median follow-up was 11.5 years (range: 2−30). Median cabergoline dose was 7 mg/week (range: 5−15 mg/week). Eight patients underwent pituitary surgery and 11 patients underwent radiotherapy (7 patients underwent both pituitary surgery and radiotherapy). Temozolomide was administered in one patient with aggressive macroprolactinoma, resistant to DA even after neurosurgery and radiotherapy, without improving prolactin levels or tumor shrinkage. None of the patients received Pasireotide. Normalization of prolactin levels occurred in 6 out of 16 patients (37.5%): in 2 patients by increasing CAB dose up to 5 and 9 mg/week, respectively and in 4 patients after pituitary radiotherapy. Two patients were cured at 9 and 10 years after high voltage radiotherapy, respectively. Two patients denied any radical therapy and are currently on high cabergoline dose (10.5 and 7 mg/week), with uncontrolled hyperprolactinemia.
Conclusion
Cabergoline dose escalation and radiotherapy can improve the outcome of macroprolactinomas resistant to DA.

DOI: 10.1530/endoabs.65.P288

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Does volumetric MRI (3D-SGE sequence) imaging enhance diagnostic rates in Cushing's disease?

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Tumour localisation in Cushing's disease (CD) can be challenging; most are microadenomas and 50% are <5 mm in diameter. They are, therefore, often difficult to detect by conventional MRI. Volumetric MRI (3D-SGE, spoiled-gradient echo 3D sequence) is a high spatial resolution scanning technique which uses very thin slices (1 mm). Theoretically, this increases the probability of finding small pituitary lesions when compared to conventional (spin-echo, SE) MRI techniques. We compared these MRI techniques in corticotroph microadenoma localisation. Twenty consecutive patients with biochemically confirmed CD underwent both conventional and volumetric MRI techniques. We excluded four patients with pituitary macroadenomas as the imaging in these patients is rarely problematic. Two patients are awaiting surgery. In the remainder, an experienced neuroradiologist (JE) classified conventional and volumetric scans as: definite lesion; equivocal lesion; normal gland. The analysis showed: In four patients, volumetric scanning revealed a lesion within a pituitary gland previously reported as normal on conventional MRI sequences. All four lesions were subsequently shown to be an ACTH-staining adenoma. In four patients, volumetric scanning was negative, with conventional imaging showing either a definite or equivocal lesion, each of which was subsequently histologically confirmed. In the other patients, volumetric scanning provided equivalent/complementary information to conventional imaging and/or the findings were equivocal and/or did not correlate with surgical findings. In the operated microadenoma patients, the remission rate was 86% (12/14). In both non-remission cases, no lesion was seen with either MRI sequence. Volumetric MRI may provide useful additional information to conventional MRI sequences to assist in surgical planning, but does not replace conventional sequences.

DOI: 10.1530/endoabs.65.P289

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The prevalence of acromegaly in the sleep apnoea clinic

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Introduction
The prevalence of acromegaly in the general population ranges 4–14/100 000. 45–80% of acromegaly patients have obstructive sleep apnoea (OSA). The OSA population might represent a target group for earlier detection of acromegaly, thereby reducing associated long-term morbidity.
Methods
Patients attending the sleep service (11/2014–04/2018) were recruited in a prospective multicentre cohort study. All had serum IGF-1 measurement and completed a screening questionnaire for five key symptoms associated with acromegaly. Those with raised age-specific IGF-1 underwent further biochemical assessment to investigate for acromegaly.
Results
1080 participants (73% male, mean age 55.6±12.0 years) with confirmed OSA were recruited across two sites. Forty-three patients (4%) reported at least 4/5 acromegaly-related symptoms. There was no correlation between serum IGF-1 and symptom score. Sixty-one patients (5.7%) had elevated IGF-1 level on initial assessment. Fifty-one had repeat IGF-1 testing, while one had growth hormone measurement of <1 μg/l. Nine patients were lost to follow-up, including one death. Of the repeat IGF-1 tests, results were normal in 24 cases and no further investigation was undertaken. Repeat IGF-1 results were unavailable in 3 cases. In the remaining 24 patients with persistently raised IGF-1, 11 had GH <1 μg/l, suggesting that acromegaly was unlikely. The remainder ($n=13$), as well as the 3 individuals with unavailable IGF-1 results, had an oral glucose tolerance test. One patient (BMI of 23.7 kg/m^2) was diagnosed with acromegaly, was diagnosed with severe OSA and reported 4/5 acromegaly-related symptoms during screening.
Conclusion
Our study identified a single case of acromegaly within the OSA population that may represent a higher prevalence than in the background population, however is based on a single case. As a consequence of the significant number of patients with elevated serum IGF-1 measurements requiring further investigation, IGF-I is not currently a cost-effective screening tool for early detection of acromegaly in OSA patients.

DOI: 10.1530/endoabs.65.P290

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ACTH producing pancreatic NET

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We present the case of a 64 year old woman who presented with one month history of tiredness and 8 kg weight loss. Severe hypokalemia (2.2 mmol/l) was identified by the GP. Clinically she appeared mildly Cushingoid. Biochemical investigations showed a random cortisol significantly elevated at 2170 nmol/l, 24-hour urinary cortisol was 15 700 nmol/l(0–135). ACTH level was elevated at 7400 ng/l(0–40). The low dose dexamethasone suppression test demonstrated failure to suppress, cortisol value > 1700 nmol/l. The clinical presentation was felt to one of a malignant process and CT chest abdomen and pelvis confirmed liver metastases, occupying approximately 75% of the liver, with no identifiable primary alesion and bilateral adrenal hyperplasia. The liver biopsy confirmed metastatic well differentiated (G1-Ki 67 of <2%) Neuroendocrine Tumour with Likely GI tract primary origin based on immunohistochenistry. A gallium Dotatate PET scan demonstrated Dotatae avid tumour in tail of pancreas, with multiple Dotatate avid liver metastasis. Considering her symptoms, initial blockade with metyrapone was attempted but was ultimately inadequate for symptom control. Somatostatin Analogues (SSA) was commenced given the DOTATATE scan results. She suffered several collapse fractures of her spine (no evidence of a malignant process were seen and this was felt to be osteoporotic in nature. Unfortunatelt the patient's symptoms and cortisol levels were not well controlled on Metyrapone and SSA, therefore bilateral adrenalectomy was felt to be necessary. As there are two surgeons locally who are able to perform adrenalectmy through a posterior approach using retroperitoneal technique she underwent a simultaneous retroperitoneal bilateral adrenalectomy. Post operatively she has good clinical improvement in her symptoms and further imaging is planned to consider if PRRT is required for disease progression. Our case demonstrates the need to review and modify treatments depending on patient's response. We believe this is the first simultaneous bilateral adrenalectomy in the UK.

DOI: 10.1530/endoabs.65.P291

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Cabergoline in the treatment of acromegaly: experience from a large pituitary centre

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Introduction
Cabergoline is one of the medical treatments in acromegaly; it can be used alone or in combination with other available agents.
Aim
To review the efficacy of cabergoline in patients with acromegaly treated in our centre.
Patients and methods
Patients with acromegaly on cabergoline were identified from our Pituitary Registry. Clinical/laboratory/imaging data were collected and analysed.
Results
Follow-up data were available for 42 patients [25 males, 16 received cabergoline monotherapy and 26 cabergoline combined with somatostatin analogue ($n=24$) or pegvisomant ($n=2$)].
Monotherapy group
10 patients had surgery and 3 radiotherapy prior to cabergoline. Median baseline (prior cabergoline) IGF-I 139% ULN (102−253%). Cabergoline dose: median 2 mg/week (0.25−4); median duration of treatment 31 months (5−107). At last follow-up: median IGF-I 112% ULN (48−160%); normal IGF-I was achieved in 7 (44%) patients. Cabergoline and somatostatin analogue group: 18 patients had surgery and 15 radiotherapy prior to medical treatment. 15 had octreotide LAR and 9 lanreotide. Median baseline (prior cabergoline) IGF-I 175% ULN (128−292%). Cabergoline dose: median 1.5 mg/week (0.5−3.5); median duration of treatment 31 months (11−117). At last follow-up: median IGF-I 136% ULN (range 64−244%); normal IGF-I was achieved in 6 (23%) patients.
Cabergoline and pegvisomant group
Both patients had surgery and radiotherapy prior to medical treatment. Median pegvisomant dose 38 mg/day (7.5−30 mg). Baseline (prior cabergoline) IGF 158% ULN (available for one patient). Cabergoline dose: median 2.75 mg/week (2−3.5 mg). At last follow-up: median IGF-I 130% ULN (110−150%); normal IGF-I was achieved in no patient. Four patients reported mild adverse effects (nausea, dizziness, or nasal congestion) whilst on the dopamine agonist.
Conclusions
In our series, cabergoline offered as monotherapy in patients with biochemically mild acromegaly was highly effective. In contrast to previous published experience, the results were less optimal when combined with somatostatin analogue treatment.

DOI: 10.1530/endoabs.65.P292

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Frequency and timing of hypopituitarism as a consequence of pituitary directed radiotherapy; a retrospective cohort study

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Background
Patients receiving radiotherapy for residual or recurrent pituitary adenoma require regular surveillance for the development of anterior pituitary axis deficit. Whilst the sequelae of hypopituitarism post cranial irradiation is well recognized, there are relatively varied incidences of new onset hypopituitarism post-conventional radiotherapy, reported in the literature. We aimed to investigate timing and frequency of the individual axis deficits in adults who have received pituitary targeted radiotherapy in our centre.
Objective/aim
To determine the rates and timing of deficit in the individual anterior pituitary hormone axes post pituitary radiotherapy.
Methods
We performed a single-centre retrospective analysis of patients receiving pituitary radiotherapy for recurrent or residual pituitary adenoma between 1995 and 2019. Eligible patients had no history of prior radiation, normal pituitary function prior to radiotherapy and at least 12 months of endocrine follow-up. We assessed the effects of pituitary radiotherapy upon endocrine function in 74 adults (44 males) receiving a dose of 45 Gy in 25 fractions for recurrent/residual pituitary adenoma.
Results
Mean age at the time of receiving RT was 53 years and the median duration of endocrine follow up was 9.1 years. Overall prevalence of radiotherapy induced hypopituitarism was 26.7%. GH, FSH/LH, TSH and ACTH deficiency were present in 24.4%, 22.2%, 20% and 22.2% of patients respectively at a median time of 8.3 years, 10.8 years, 9.3 years and 9.3 years respectively. Rate of new axis deficit was 8% at 2 years, 20% at 5 years and 27% at 10 years.
Conclusion
Our data reiterate the need for lifelong endocrine follow-up of patients receiving pituitary radiotherapy with 15% patients developing new axis deficit at >10 years post RT. Knowledge of frequency and timing of pituitary deficit is important when counselling patients regarding the potential risks of radiotherapy. Further analysis of new radiation techniques and long-term hypothalamic−pituitary dysfunction is needed.

DOI: 10.1530/endoabs.65.P293

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A rare case of a malignant prolactinoma presenting with skull metastasis after two years of a masked diagnosis

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Background
Pituitary carcinoma is extremely rare and constitute only 0.1−0.2% of all pituitary tumors. Diagnosis is on evidence of metastasis, although these criteria has been challenged. Majority of pituitary carcinomas are functioning tumours, usually secreting ACTH (42%) or prolactin (33%). Common sites of metastasis include the brain, spinal cord, leptomeninges, bone, liver, lymph nodes and lung. Mean survival after detection of metastasis is around 1−2 years.
Case history
A 68 year-old-lady, known to have resistant macroprolactinoma for 10 years, but not seen over the last year, presented with a progressively enlarging 3 cm occipital scalp lump over 6 months duration. In the past she refused surgery, therefore she was treated with cabergoline 7 mg/week and pituitary radiotherapy in 2014. Her prolactin was 851 mIU/l post-radiotherapy and one year later it has risen to 123 340 mIU/l without significant change in her pituitary lesion. CT showed an erosive soft tissue mass arising from the dura and encompassing the full thickness of the bone and the scalp lesion. Biopsy revealed pituitary tissue with positive prolactin staining and a high Ki-67 (27%) with p53 positivity confirming the diagnosis of pituitary carcinoma. Retrospective analysis of MRI scans of the preceding 2 years revealed the emergence of a small occipital dural metastasis, which was not noted by the radiological reports. Bone scan revealed multiple vertebral and bone metastasis. Patient received temozolmide and radiotherapy to three areas with metastatic lesions. She had a marked clinical (lesion size <1 cm) and biochemical (prolactin 2024 mIU/l) response over next 12 months. She died 2 years after the diagnosis of the metastasis.
Conclusion
Pituitary carcinomas can have rare clinical presentation with dural metastasis causing a large lesion in the skull. Significant increase in prolactin levels without change in size of an invasive macroprolactinoma may raise the suspicion of metastasis. Early diagnosis of metastasis could lead to initiation of temozolamide and radiotherapy.

DOI: 10.1530/endoabs.65.P294

P295

Review of pituitary metastases diagnosed in a large pituitary centre

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Background
Metastatic disease in the pituitary (PM) is uncommon and the published literature mainly involves case reports and small case series. We aimed to analyze presenting manifestations and outcomes of patients diagnosed with PM in our pituitary centre.
Methods
Retrospective review of our Pituitary Registry to identify patients with PM from 2006 to present. Clinical, radiological, and pathological data were collected and analysed.
Results
We identified 19 patients (13 F) with the diagnosis of PM. 8 had histologically proven PM and the others were diagnosed clinically. The presenting manifestations were visual dysfunction (cranial nerve palsies or visual fields compromise) in 8 patients, hypoadrenalism in 2, diabetes insipidus (DI) in one, and headache in one; in 7 patients, PM was detected on imaging without associated clinical manifestations. Twelve patients were diagnosed with hypopituitarism at presentation, though only 3 had DI. The majority of patients ($n=13$) had a known diagnosis of malignancy at the time of PM detection (median time between primary malignancy and PM diagnoses 29 months, range 10−240). The most common primary malignancies were lung ($n=7$) and breast ($n=6$); prostate ($n=2$), melanoma ($n=2$), glioblastoma ($n=1$), and renal carcinoma ($n=1$) were the remaining tumours. Management strategies for the PM included radiotherapy ($n=8$), surgery and radiotherapy ($n=4$), surgery alone ($n=3$) or monitoring ($n=4$). One-year survival following PM diagnosis was 42%.
Discussion/conclusions
PM has variable clinical presentation. Some findings from our series differ from previous literature. We report several asymptomatic PMs detected on imaging. Most patients had evidence of hypopituitarism, but DI was relatively uncommon. Although, PM has previously been considered a manifestation of end-stage malignancy associated with very short life expectancy, one-year survival in our series was higher than reported in most previous literature, possibly reflecting improvements in the management of the primary cancer.

DOI: 10.1530/endoabs.65.P295

P296

In-hospital endocrinology consultation (IHEC) for patients undergoing transsphenoidal resection of sellar masses – is it always necessary?

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Patients with sellar masses (SM) undergoing transsphenoidal surgery (TSS) have a significant risk of transient or permanent endocrine dysfunction; therefore, in-hospital endocrinology consultation (IHEC) is recommended for these patients. However, routine assessment of all TSS patients by a specialized team is not feasible outside select centers. We developed an IHEC guide for TSS patients in December 2015 to identify those patients who would require perioperative IHEC. We conducted a retrospective analysis of all patients who underwent TSS between January 1, 2016 and December 31, 2017 to assess the predictive value of the IHEC guide in identifying patients who required IHEC and also its impact on the in-hospital and immediate post-operative endocrine complications. Seventy seven patients (41 males; mean age: 57.9 + 1.75 years and the mean tumour volume: 7.48 + 1.02 ml) underwent TSS. Of these, 17 (22%) patients required IHEC based on the IHEC guide. The mean age, tumour volume and indications for TSS were similar in IHEC and non-IHEC patients. The primary indication for IHEC was the risk of diabetes insipidus in 12 (70%) patients and the IHEC compared with non-IHEC patients had longer hospital stay (8 days vs. 3 days), higher rate of new post-operative hormonal deficit (70% vs. 0%), higher 30-day readmission rates (23% vs. 11%) and higher rate of secondary adrenal insufficiency (70% vs. 26.7%) [$P=0.001$]. In the non-IHEC group, only 1 out of 60 patients developed new-onset hormonal dysfunction (NPV = 0.97; 95% CI = 0.9155–0.9918) whereas in the IHEC group 12 out of 17 developed new-onset hormonal; (PPV=0.82; 95% CI of 0.7333–0.8830) during perioperative or immediate post-operative period. Our data indicate that around three quarters of TSS patients can be managed safely without IHEC with no evidence of compromise of hormone-related care.

DOI: 10.1530/endoabs.65.P296

P297

Outcomes in patients undergoing transsphenoidal surgery for non functioning pituitary macroadenomas at Lancashire Teaching Hospitals NHS Foundation Trust

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Non-functioning pituitary macroadenomas (NFPAs) are commonly associated with headaches, visual deficits and hypopituitarism. Urgent transsphenoidal surgery (TSS) should be considered for all patients presenting with visual compromise. We evaluated outcomes in 65 patients with NFPAs undergoing TSS in our unit. Patients who had undergone previous pituitary surgery or prior radiotherapy were excluded from this evaluation, as were those with classical pituitary apoplexy and predominantly cystic lesions. The majority of patients were male ($n=46$; 70.8%) and mean age at the time of surgery was 57 years (range 28−88). Preoperatively, information on formal visual testing was available for 64 patients; 51 (79.7%) had visual compromise. Of these 51, pre- and postoperative comparison was possible in 50 patients and all showed some degree of visual improvement following TSS. For the 13 patients with normal vision preoperatively, outcomes of postoperative visual testing were unavailable in 2; in the remaining 11, vision remained normal postoperatively. There was no deterioration in vision in any patient. Subjective visual impairment was reported by 43 patients preoperatively, with improvement in 95.3%. In 50 of 61 patients (82.0%), preoperative hypopituitarism (at least one pituitary hormone deficit) was evident; gonadotrophins 41/57 [71.9%], TSH 37/62 [59.7%] or ACTH 15/54 [27.8%]. Increasing quartile of tumour volume was associated with increased prevalence of preoperative hypopituitarism (OR=2.15, $P=0.039$). Postoperatively, a new hormone deficiency in any axis occurred in 12 of 54 (22.2%) of patients, with hormone recovery in any axis in 17 of 50 (34%) of patients with preoperative deficiency. The ACTH axis demonstrated the greatest propensity for recovery postoperatively; 26.7% of patients had full or partial improvement in ACTH production (TSH 24.3%, Gonadotrophins 12.2%). In conclusion, TSS was associated with a good subjective and objective visual outcome for patients. Endocrine improvement in at least one axis occurred in a third of patients with preoperative hypopituitarism.

DOI: 10.1530/endoabs.65.P297

P298

Review of microarray, RNA sequencing and next-generation sequencing data reveals key pathways involved in pituitary tumorigenesis

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Background
Pituitary adenomas are the most common intracranial neoplasm, with a slow-growing, locally invasive phenotype. Some result from syndromes or isolated germ-line mutations, while approximately 60% have no currently identified somatic mutation implicated in tumorigenesis. High throughput technologies such as microarray, RNA sequencing (RNAseq) and next-generation sequencing (NGS, incorporating whole genome- and exome sequencing) have recently been used to identify altered genes and pathways involved in tumorigenesis.
Aims
To perform a comparative analysis and literature review of microarray, RNAseq and NGS studies into human pituitary tumours.
Methods
Ovid MEDLINE and EMBASE databases were searched in a systematic method (to May 2019) and relevant papers selected. Included papers assessed human pituitary adenomas of any hormonal profile using high throughput sequencing technology. Targeted approaches, previously identified somatic mutations, and non-coding RNA studies were excluded. 35 papers were reviewed in total.
Results
One new recurring somatic mutation in corticotrophomas, *USP8*, was identified using whole exome sequencing. One previously identified mutation in somatotrophinomas, *GNAS*, was also noted. Key pathways were noted as differentially enriched, including Wnt and Notch signalling, epithelial mesenchymal transition (EMT) and extracellular matrix adhesion (ECM). Microarray technology is the most common high throughput technology in use, with NGS and RNAseq in use for the last six years.
Conclusion
High throughput technologies have developed recently, with whole exome and genome sequencing becoming more ubiquitous. These technologies may be more useful for identifying differentially enriched pathways than for singular recurrent somatic mutations. The pathways identified have clear roles in tumorigenesis and pituitary development and are potential targets for novel therapeutic agents and further research. Future research may assess the findings of non-coding RNA studies.

DOI: 10.1530/endoabs.65.P298

P299

Use of serial Short Synacthen tests (SST) in determining failure of hypothalamic–pituitary – adrenal (HPA) axis in patients with pituitary disorders

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Introduction
The study aim was to compare serial Short Synacthen test (SST) results to diagnose secondary Adrenal Insufficiency (AI) in patients with confirmed pituitary diseases.
Methods
Serial SST results of patients, tested between 2006 and 2018 in the department of Diabetes and Endocrinology, at a tertiary centre, were reviewed retrospectively. Patient details were obtained from local dynamic test database, maintained by Endocrine Nurse Specialist. SST results were included only if patients had pituitary disease and underwent SST more than once. Details of surgical and radiotherapy interventions were obtained. Assay specific cut-offs were applied and appropriate cortisol responses recorded at 30 and 60 min. Results were interpreted as pass if either 30 min or 60 min or both values were above cut-off excluding secondary AI. Results were paired with baseline and final values based on either 30 min only or combined 30 and 60 min SST results to diagnose failure of HPA axis.
Results
A total of 118 patients underwent 465 SSTs (mean 3.94 tests / patient). There were 60 males and 58 females. Fifty one patients underwent Pituitary surgery and 52 received Radiotherapy. At baseline, 78/118 (66%) patients passed the test which included 15/118 (12%) patients showing suboptimal response (failed) at 30 min and satisfactory response (passed) at 60 min. On final assessment, 87/118 (73%) patients showed intact HPA axis both at 30 and or 60 min, while 31/118 (26%) failed the test with suboptimal response at 30 and 60 min. Out of 87/118 patients who passed the test, 11/118 (9%) would have been started on corticosteroid therapy, if only 30 min values were used.
Conclusion
The study suggests that measuring both 30 and 60 min cortisol levels during SSTs can avoid initiation of corticosteroid replacement therapy in some patients. Further large scale studies are needed to validate our findings.

DOI: 10.1530/endoabs.65.P299

P300

Oxaliplatin/raltitrexed-associated nephrogenic diabetes insipidus – a new finding

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Background
Nephrogenic diabetes insipidus (DI) is characterized by polyuria with dilute urine due to the inability of the principal cells of the renal collecting ducts to respond to antidiuretic hormone and concentrate urine. It can be drug-induced and several chemotherapeutic agents, including the platinum derivative cisplatin and the antimetabolite pemetrexed, have been reported to cause nephrogenic DI, presumably via tubular damage.
Case presentation
A 63-year-old man with stage III colonic cancer, angina, ischaemic heart disease and hypertension had received five cycles out of six planned adjuvant chemotherapy with oxaliplatin and raltitrexed post bowel surgery. He presented with nausea, vomiting and increased frequency of urine. Serum sodium was 157 mmol/l, creatinine 124 μmol/l (acute kidney injury stage 1). He was given intravenous fluids to correct his presumed pre-renal AKI. However, both his serum sodium and urine output remained high. Full body CT scan with contrast reported no evidence of disease and his renal screen came back negative for autoantibodies. After ten days serum sodium was 150 mmol/l, creatinine 179 μmol/l, serum osmolality 304 mOsm/kg and urine osmolality 184 mOsm/kg with urine output >3 l/day. On a vasopressin challenge test, urine osmolality rose but only to 292 mOsm/kg. This suggested nephrogenic DI. He had normal pituitary imaging. He was treated with high dose desmopressin with slight improvement in polyuria, and more successfully with bendroflumethiazide. His sodium level and serum osmolality have come back within normal range and creatinine has improved. His final cycle of chemotherapy was omitted.
Conclusion
To the best of our knowledge, this is the first reported case of nephrogenic DI after oxaliplatin and raltitrexed. It is not clear whether the combination of two agents from classes known to be associated with DI may increase the risk.

DOI: 10.1530/endoabs.65.P300

P301

The natural history of pituitary apoplexy: long term follow-up study

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Introduction
Pituitary Apoplexy is a rare endocrine emergency which can occur due to infarction or haemorrhage of pituitary gland. Pituitary apoplexy can occur as an initial presentation in patients who are not known to have Pituitary adenomas. Clinical Symptoms vary, however, one should have a high index of suspicion if symptoms such as acute headache, visual loss or ocular palsy occur.
Precipitating factors
Hypertension, Preganancy, Head trauma, Dynamic testing of pituitary gland.
Methods and aims
The clinical data of all patients attending the Morriston Hospital pituitary clinic are recorded on leicester, a computerised database. A search revealed 43 patient from 1998 to date. Data was obtained from the database and clinic letters. Our aims: Pituitary adenoma causes, Previous history of Pituitary adenoma or first presentation, Management, Long term follow up and complications.
Results
Among 43 patients, 47% were male with the mean age of 60.4 years at presentation. Of these patients 3 had acromegaly, 1 had Cushing's Disease, 2 had Macroprolactinoma, 3 had malignant secondaries and 1 had craniopharyngioma.

The remaining 29 patients had non functioning adenomas. Among these patients 24 (37%) were not previously known to have a pituitary tumour. 15 (37%) presented with external ophthalmoplegia and 10 (23%) with visual loss. 5 (11%) presented with sudden blinding headaches and 12% with Nerve palsy. 17 patients had surgery of which 8 patients had radiotherapy. 2 only had radiotherapy purely due to the size of the tumour. The remainder were managed conservatively. Majority of patients developed hypopituitarism. Only 1 patient with chromophobe adenoma had a significant second episode of apoplexy requiring repeat surgery.
Learning points
Pituitary apoplexy is a rare endocrine emergency. Commonly occurring as first presentation in patients with unknown pituitary adenoma. External ophthalmoplegia recovered in all cases. Hypopituitarism is a common complication. Recurrence of pituitary apoplexy is rare.

DOI: 10.1530/endoabs.65.P301

P302

Macroprolactinoma resistant to cabergoline: effective use of quinagolide

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Prolactinomas are the most common functional pituitary tumours. Therapy is with dopamine agonists (DA). Cabergoline is frequently used as a first line agent; resistance to therapy is seen to other DA. We present a case of a 32 year old woman who moved to our area in the 1st trimester of pregnancy. She was known to have macroprolactinoma (maximal diameter > 1 cm), impinging on the optic chiasm. She was on cabergoline 0.5 mg once daily, but this was discontinued with no complications during pregnancy. Cabergoline 0.5 mg weekly was restarted 9 months postpartum, but serum prolactin remained elevated (5768 mIU/l; Normal Range: 102–496) and titration to 1 mg twice a week reduced this to 4054 mIU/l. Compliance was good. Therapy was changed to quinagolide rather than further increase in cabergoline dose, and a daily dose of 150 mcg reduced serum prolactin to 106 mIU/l. There was no change in the size of the adenoma on MRI, but there was no longer any impingement on the optic chiasm. Both quinagolide and cabergoline are selective D2 receptor agonists. Cabergoline resistance (which can be described as lack of response to a weekly dose $\geq$ 2 mg) is uncommon and tends to occur in macroprolactinomas. Increasing the dose further may prove effective, but carries an increased risk of side effects. Patients resistant to bromocriptine or quinagolide have been successfully treated by using cabergoline instead. This is the first case to our knowledge of a macroprolactinoma resistant to cabergoline, but responding to quinagolide.

DOI: 10.1530/endoabs.65.P302

P303

Thyrotropic adenoma requiring transphenoidal surgery in a young female with congenital hypothyroidism

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TSH-secreting pituitary tumours are very rare and include two opposite clinical conditions: true thyrotroph neoplasia resulting in secondary hyperthyroidism /central hyperthyroidism and pituitary hyperplasia resulting from longstanding primary hypothyroidism. The diagnosis is suspected in patients presenting with headache / biochemical hyperthyroidism high free T4, free T3 and unsuppressed TSH concentrations, particularly in the presence of clinical features of concomitant hypersecretion of other pituitary hormones. However thyrotroph adenomas in long standing hypothyroidism are rare with very few reports on congenital hypothyroidism as primary underlying disease. We present a case of 21 yearr old female who presented with amenorrhoea after removal of contraceptive implant. No symptoms of galactorrhoea. Endocrine investigation: elevated Prolactin 1254 mU/l (102–496 mU/l), with normal LH, FSH & oestrodial, TSH >100, Cortisol 430 nmol/l and IGF-1 below normal reference range. Past medical history: congenital hypothyroidism with long standing poor compliance with levothyroxine therapy. MRI pituitary revealed macroadenoma with suprasellar extensions with chiasmatic compression and carotid sinus invasion. Her raised serum prolactin was thought to be related to stalk effect. She started experiencing severe headaches – worse on sneezing / coughing. As the adenoma was causing chaismatic compression and she was planning to start family soon, following discussion in the regional pituitary MDT, she underwent transspheniodal surgery. The histology revealed nodular expression of prolactin with evidence of thyrotrope hypertrophy. Postoperatively, MRI pituitary showed no evidence of recurrence of pituitary tumour. This is an extremely unusual case of extreme thyrotropic adenoma requiring surgery. Such thyrotropic adenomas of the pituitary gland are presumed to occur as a result of protracted pituitary stimulation secondary to long-standing thyroid deficiency. Nodular hyperplasia or occasionally a TSH-secreting pituitary tumor can arise in a hyperplastic gland. Future diagnosis and treatment of this rare disorder depend on the recognition of the genetic basis leading to tumor development.

DOI: 10.1530/endoabs.65.P303

P304

Pituitary imaging in mild hyperprolactinaemia

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Background
Hyperprolactinaemia is a common presentation in endocrine clinics. Current guidelines on BMJ best practice recommend evaluation with MRI only if levels are >2000 mU/l or absence of an identifiable secondary cause.
Aim
To identify if pituitary pathology would go undetected if pituitary imaging is not performed and determine a suitable threshold for performing pituitary imaging in the diagnosis of prolactinoma.
Methods
A retrospective study on 100 new patients with raised prolactin level below 1000 mU/l (17–75 years old) over 12 months (Jan–Dec 2017).
Result
33 male and 67 female studied. 16% of patients had prolactin level of 350–500 mU/l, 54% with prolactin level of 500–700 mU/l and 30% between 750–1000 mU/l. Menstrual irregularities were the most common symptoms (22%) followed by Erectile dysfunction/Gynaecomastia (16%), headache (10%). Fatigue 8%, subfertility 6% and galactorrhoea 5%. 33% were asymptomatic. MRI pituitary was performed on 60 patients and CT head on 2. MRI pituitary gland identified 17 microadenoma, 3 pituitary cysts, and 2 empty Sella. 40 had normal MRI and CT finding.
Conclusion
22 out of 62 (35%) patients had positive findings on MRI scan with mean initial prolactin level of 640 mU/l which based on current guidelines would not require pituitary imaging. With such a high pickup rate clinical as well as biochemical criterion should be applied to patient selection for imaging. The majority of lesions identified will be incidental but may benefit from followup.

DOI: 10.1530/endoabs.65.P304

P305

Can a hypernatraemia alert system protect inpatients with diabetes insipidus?

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Background
Over the past decade there has been increased recognition of the dangers associated with inpatient management of diabetes insipidus (DI) and omission of desmopressin leading to hypernatremia. In May 2009 a patient died from diabetes insipidus mismanagement in a London hospital. An NHS England patient safety alert was issued in 2016 highlighting this risk.
Method
Inpatients with a serum sodium of 155 mmol/l or greater were prospectively identified on a daily basis over a period of six months. A semi-automated report was generated but not circulated or acted upon at the time. After 6 months the reports were retrospectively reviewed to assess the outcomes of these patients and

to assess whether real time review of this data would have led to a change in management. We also assessed: cause of hypernatraemia, action taken, involvement of the endocrine team and outcome including 30 day mortality.
Results
After excluding paediatric cases and patients in intensive care: 87 patients were identified over 6 months. The age range was 33–92 with mean age 72. The serum sodium ranged from 155–178, mean 160 mmol/l. 2% of the cohort (2/87) represented decompensated diabetes insipidus. The mortality of the overall cohort was high, 48% (42/87) died either during the admission or within 30 days of discharge. 26% (23/87) of cases were referred to the endocrine team for inpatient review.
Discussion
Inpatient severe hypernatraemia (Na $\geq$ 155) is uncommon but the associated mortality is extremely high. Automated surveillance would alert the endocrine team to 100% of patients with severe hypernatraemia, as opposed to the 26% of cases currently referred. Annually a small number of cases of decompensated inpatient diabetes insipidus could potentially be identified by this method of surveillance, which may have patient safety benefits.

DOI: 10.1530/endoabs.65.P305

P306

Long term effects of cranial radiotherapy on hypothalamic–pituitary–adrenal axis in patients with established pituitary diseases

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Introduction
Radiotherapy is an important adjuvant treatment for pituitary and cranial diseases. The aim of the study was to observe response of Radiotherapy (RTX) on Hypothalamic–Pituitary–Adrenal (HPA) axis determined by serial Short Synacthen tests (SSTs).
Methods
Patients treated with adjuvant Cranial Radiotherapy between the years 2000 and 2018 in the department of Radiation Oncology and who also underwent serial Short Synacthen tests, in the department of Endocrinology, in a tertiary care centre, were reviewed retrospectively. Patient details were initially obtained from local dynamic test database, maintained by Endocrine Nurse Specialist. Details of total radiation doses in Grays (Gy) were provided by Radiation Oncology department. The patients underwent serial SSTs to assess HPA axis before and after radiotherapy. Assay specific cut-offs were measured for cortisol responses at 30 and 60 min to interpret results as either pass or fail. Cortisol levels at 30 min or 60 min or both below cut-offs resulted in diagnosis of secondary Adrenal Insufficiency (AI) leading to initiation of corticosteroid replacement therapy.
Results
In total, 32 patients received adjuvant radiotherapy (mean dose 44.5 Grays, median 35–60 Grays) between the years 2000 and 2018. These doses were delivered in 25 to 40 fractions over 29 to 40 days. Twenty patients underwent Pituitary surgical interventions. A total of 169 SSTs were performed before and after radiotherapy. Intact HPA axis was observed in 21/32 (65%) patients, while in 11/32 (34%) patients there was sub-optimal response after mean duration of 7.6 years (median 1–20 years) consistent with secondary AI.
Conclusion
The findings of the study showed HPA axis failure in one third of the patients who received cranial radiotherapy for pituitary or cranial diseases. Further large scale studies are needed to validate our findings.

DOI: 10.1530/endoabs.65.P306

P307

A case of SIADH post-brain injury presenting in pregnancy

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Introduction
Syndrome of inappropriate anti-diuretic hormone (SIADH) is the one of the most common causes of hyponatraemia encountered in hospitalised patients. However, there are very few reported cases of SIADH in pregnancy. This case describes such an entity.
Case Report
A 21 year old lady who was seven weeks pregnant presented to hospital following episode of new onset seizure. She was involved in a road traffic accident seven months prior with associated brain injury. Her blood test revealed new hyponatraemia. Clinically, she was euvolaemic. Biochemistry confirmed a picture of SIADH. Levetiracetam and fluid restriction of one litre a day was commenced. She responded well to fluid restriction with her sodium improving gradually and was discharged with regular follow up at Joint Endocrine/Obstetric Antenatal clinic. Her sodium was maintained in the normative range with 1–1.25 l daily fluid restriction except on the odd occasions when she did not keep to strict fluid restriction but her sodium did not drop lower than 130 mmol/l. Induction of labour was performed at 37 weeks gestation due raised dopplers and small for gestational age foetus. Her sodium dropped to 125 mmol/l on admission. To ensure strict and accurate fluid restriction, she was commenced on one litre intravenous fluid 24 hourly and kept nil orally. This improved her sodium and she delivered a small but healthy baby girl with weight on the third centile. She remained seizure free throughout. Four months *post-partum*, with fluid restriction, her sodium remains normal.
Discussion
Fluid requirement in normal pregnancy is around 300 ml/day higher than non-pregnant women. This provides a challenge in managing SIADH in the context of pregnancy. Very little guidance is available in managing these patients. Our experience has shown that fluid restriction to around one litre daily in pregnancy for SIADH seemed safe.

DOI: 10.1530/endoabs.65.P307

P308

Making best use of clinical genetic testing in the diagnosis of Neurohypophysial Diabetes Insipidus with significant family history – a case for early access

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Background
Familial Diabetes Insipidus is a very rare entity and can have either neurohypophyseal (FNDI) or nephrogenic forms with different transmission patterns. FNDI accounts for less than 5% of the 1:25 000 cases of DI diagnosed in UK. It is usually an autosomal dominant disorder caused by mutations in AVP (arginine vasopressin) gene, which regulates the vasopressin hormone synthesis; its signs and symptoms of polyuria & polydipsia usually become apparent in childhood and worsen over time.
Case presentation
We describe the case of a 46 years old female presenting with polydipsia 20–30 l of fluids/day, polyuria and nocturia 3–6 times per night ever since early childhood. She had very convincing similar family history in all generations on her paternal side, affecting nine first- and second-degree relatives, however no formal diagnosis was previously attempted. Initial biochemistry results showed dilute urine at 77 mOsm/kg, serum osmolality 295 mosm/kg, otherwise normal pituitary hormones. Patient had supervised water deprivation test (WDT), during which serum osmolality rose to 302 mOsmol/kg after one hour, with urine osmolality of 74 mOsmol/kg. 2 ug desmopressin administration intramuscularly achieved good but incomplete concentration in urine osmolality to maximum of 436 mOsm/kg at 4 h. Patient commenced desmopressin tablets with good symptomatic response on a total split dose of 300 mcg daily. Considering the significant family history, her son was offered endocrine testing and WDT, with a view to formal molecular genetic testing being considered subsequently.
Conclusion
WDT causes apprehension in children and parents, which often delays presentation to medical services and appropriate treatment initiation. The utility of genetic testing in confirming underlying familial CDI has previously been acknowledged, even in the absence of definite biochemical features. Its advantages include appropriate family counselling as well as affordable cost, and clinicians should be aware of benefits of early access to this for affected family members.

DOI: 10.1530/endoabs.65.P308

P309

Post trans-sphenoidal pituitary surgery outcomes: single centre, single surgeon outcome data

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Introduction
Transsphenoidal pituitary surgery (TSPS) may be required either as a treatment for endocrinopathies or because of the risk or consequence of pituitary lesion expansion into adjacent structures, in particular optic chiasm compression. Published literature recommends surgery is performed by dedicated experienced surgeons with anticipated complication rates available as a comparator.
Methods
This retrospective audit included all patients diagnosed with a pituitary adenoma at Heartlands Hospital who subsequently had TSPS at University Hospital Coventry between 2012 and 2018. Data on endocrine, visual and operative complications was recorded and compared to assessment prior to TSPS.
Results
Of the 45 included patients the majority had non-functioning adenomas (NFA) (60%), additional surgical indications including acromegaly (24%), Cushing's disease (2.4%) and macroprolactinomas not sufficient responsive to medical management (6.62%). 84% of adenomas were macroadneomas radiologically and 78% had normal anterior pituitary profile pre-op and 63% had normal fields. 40% developed a new anterior pituitary profile deficiency post-op and 13% developed transient diabetes insipidus. 4% developed new visual field defect, 7% had residual remnant, 7% had a new neurological deficit (external ocular nerve palsy, partial right 3rd nerve palsy), 2% epistaxis, 7% headache, 2% CSF leak and 2% post-surgical bleed. 64% did not develop any complications.
Conclusion
This data shows the advantage of a single surgeon service given the comparatively low complication rates seen compared to national and international comparator data. This audit is an important component of ongoing reflective surgical practise as well as providing support for our centre's patient-based discussions of peri-operative risks.

DOI: 10.1530/endoabs.65.P309

P310

An audit of Acromegaly patients managed in a large district general hospital

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Acromegaly is a relatively rare disorder with a prevalence of 40 per million. Diagnostic and management process have evolved with time, however lack of statistical facts/data remained an issue.
Aims
1) To look at the cohort of patients who attend our local Endocrine department with a diagnosis of acromegaly. 2) To determine how many are cured with surgery, how many need adjuvant treatment and how many remain uncontrolled despite all treatment modalities. 3) Assess whether there is any biochemical or anatomical differences in how the patients in different groups initially present.
Methods
Data was collected retrospectively through a search on our trust electronic records- DIABETA3, ICE, EPRO and also patient notes. We identified 48 patients (26 male, 22 female) diagnosed between 1976 and 2018 Our local district general hospital covers a population of 675,000. IGF-1 and Growth hormone profile were available in 38 patients. There is no correlation between initial IGF-1 levels and cure rates. Only 6 patients were on hydrocortisone, 2 on thyroxine and 8 on testosterone replacement at diagnosis. 40 patients underwent surgery (23 male, 17 female). Surgery was curative in 15 patients (7 male, 8 female). Full data was available on 13 patients. 6 patients were cured (3 macro, 3 microadenoma) 7 patients were not cured (5 macro, 2 microadenoma). Tumour size does not appear to influence surgical outcome. As per all retrospective studies, our data collection was limited by missing biochemistry records, unrecorded diagnosis and patients who were diagnosed at the pre electronic database era.
Conclusion
This is one of few studies reporting key results on epidemiology, treatment options, surgical outcomes, long term mortality and morbidity. Post auditing, we have now set up a dedicated Acromegaly clinic to monitor these cohort of patients with a life-long condition. It also allows better understanding and interactions among patients with Acromegaly.

DOI: 10.1530/endoabs.65.P310

P311

Intrasellar cyst masquerading as empty sella syndrome: history repeating itself

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A 57 year-old gentleman with uncomplicated Type 2 Diabetes Mellitus and 30 pack year smoking history was assessed in outpatient endocrinology clinic with a 4 month history of non-specific symptoms, including dizziness, lack of energy and intermittent bi-frontal headaches described as 'pressure behind the eyes'. There was no history of exogenous steroid use. Bloods at 0833 h identified deficiency in testosterone (<1 nmol/l; $N=$ 6–30 nmol/l), thyroxine (free T4 6.8 pmol/l; $N=9$–19 pmol/l) and cortisol (<27 nmol/l). Prolactin was raised (884 nmol/l; $N=73$–407 mU/l). To our surprise, MRI Pituitary with contrast reported empty sella syndrome due to appearances of chronic expansion of the sella, cerebrospinal fluid (CSF) within this space and a thin looking pituitary gland. The patient was managed conservatively with hormone replacement. Following Pituitary Multidisciplinary Team evaluation, a revised diagnosis of intrasellar cyst was made due to a thin cystic wall apparent following careful inspection of the MR images. The patient awaits surgical assessment for definitive management. Cystic lesions within the sellar region are classified by site of origin (sella, suprasellar or infrasellar), tissue of origin, and histological appearances (commonly Rathke's cleft cysts or arachnoid cysts). Sellar cystic fluid signal intensity on T1WI and T2WI are equal to CSF, non-enhancing and diffusion negative and therefore present diagnostic challenges, particularly when this cyst is confined to the sellar. Varying degrees of pituitary dysfunction have been reported with sellar cysts. We echo the concerns made by Topliss and colleagues in 1977, recommending caution when evaluating an empty sella on neuroimaging. MRI is considered gold standard and experts recommend using a dedicated sella protocol which minimises the risk of missing sellar cysts. CT cisternography has been suggested as a useful adjunct to overcome this rare but important issue. With advancing neuroimaging technologies we hope future cases don't re-appear in the literature in another 4 decades time.

DOI: 10.1530/endoabs.65.P311

P312

A case of retroperitoneal fibrosis on low dose Cabergoline

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66 year old patient was diagnosed with macroprolactinoma and started on treatment with Cabergoline at a dose 250 μg twice weekly. Initial echocardiogram was normal and CT chest showed clear lung fields except mild left upper zone consolidation. During a routine follow up appointment 8 months after the initiation of treatment, the blood tests showed abnormal renal function and prolactin level was controlled. CT KUB showed features suggestive of retroperitoneal fibrosis leading to bilateral hydronephrosis requiring bilateral ureteric stent insertion. Following additional investigations guided by the renal MDT team, a conclusion was reached that retroperitoneal fibrosis was secondary to Cabergoline treatment. Patient was switched to Quinagolide but did not receive steroids. A CT scan performed 3 months following the cessation of cabergoline

showed partial resolution of Retroperitoneal fibrosis reinforcing the above conclusion. Although cabergoline is associated with pulmonary, cardiac and retroperitoneal fibrosis, current consensus is that these complications occur at higher doses used to treat Parkinson's disease and not reported in treatment of prolactinomas. Current literature does not show an excess risk of fibrotic reactions during treatment with cabergoline at a dose of less than 2 mg a week. Current advice is to obtain echocardiogram before the initiation of treatment and to arrange annual cardiac exams if the above dose is exceeded. There is no guidance on monitoring of renal function. Our case suggests possibility of developing Retroperitoneal fibrosis on treatment with small dose of cabergoline for a relatively short time. It argues the point for including baseline renal function prior to initiation of treatment and monitoring thereafter irrespective of dose of the Cabergoline used.

DOI: 10.1530/endoabs.65.P312

P313

Prolactinoma causing visual disturbance in pregnancy – a multidisciplinary management conundrum

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A 33 year old primip presented to the local ophthalmic hospital at 34 + 4 weeks' gestation with two weeks of blurred vision. Examination revealed a bitemporal hemianopia and reduced visual acuity. She was previously fit and well, and a pre-eclampsia screen was negative. An MRI scan demonstrated a haemorrhagic pituitary lesion extending into the suprasellar cistern with mild compression of the optic chiasm. Pituitary function tests showed a raised prolactin 3844 mU/l, isolated hypothyroxinaemia (TSH 2.16 miU/l, fT4 8.4 pmol/l), evening cortisol of 264 nmol/l, LH 0.2 iU/l, FSH < 0.1 iU/l and oestradiol 63 676 pmol/l. She was commenced on cabergoline 500 mcg after discussion between the endocrine and neurosurgical teams in an immediate medical attempt to relieve pressure on the optic chiasm. In view of her low T4 she commenced thyroxine 50 mcg and prednisolone 5 mg for safety. However, after 10 days of cabergoline treatment, despite a reduction in prolactin to 1140 mU/l, a significant quadrantanopia and acuity defect remained. With the need for neurosurgery increasing, and after discussion with the obstetric team, she underwent induction of labour. She had a successful vaginal delivery at 36 + 2 weeks gestation. As the bitemporal quadrantanopia persisted postpartum (with continued elevation of prolactin at 1232 mU/l), she underwent stereotactic endoscopic transphenoidal hypophysectomy 6 days post-partum. This completely resolved her visual field and acuity defect. Five days post-operatively her prolactin was 191 mU/l, 0900 h cortisol 230 nmol/l, TSH 0.54 iU/l and fT4 16.6 pmol/l. She was therefore weaned off thyroxine and cortisol. Histology demonstrated a sparsely granulated lactotroph staining adenoma with Ki67 of 2%. This case demonstrates the multidisciplinary challenges in the management of pituitary lesions in pregnancy. Clinical acumen is essential, as well as cautious interpretation of pituitary hormone levels in the absence of robust, trimester-specific reference ranges for pituitary hormones. Decisions require consideration of the risks and benefits to both mother and fetus, and demand an effective multidisciplinary approach.

DOI: 10.1530/endoabs.65.P313

P314

Resolution of symptoms of acromegaly in pregnancy

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Background
Acromegaly is rarely encountered in pregnancy and the lack of data for clinical outcomes limits the development of evidence-based guidelines. We present the case of a pregnancy in a 31-year-old woman with acromegaly due to a pituitary microadenoma.

Clinical case
The patient underwent trans-sphenoidal hypophysectomy in 2015 at the age of 28, which was non-curative: post-operative IGF-1 was 533 mcg/l (72–259 mcg/l) (down from 894 mcg/l preoperatively) and pituitary MRI showed a persistent pituitary mass (5 × 6 × 7 mm). She remained on hydrocortisone and attempts for a Short Synacthen Test had failed due to needle phobia. She became pregnant in late 2017. Her most recent IGF-1 level pre-pregnancy was 303 mcg/l and she remained symptomatic with sweats and soft tissue swelling at time of first endocrine review at 12 gestational weeks. As pregnancy progressed, her symptoms entirely resolved and IGF-1 levels fell to 21 mcg/l at week 13. IGF-1 levels rose progressively to 234 mcg/l at week 24 and 286 mcg/l at week 33 but she remained asymptomatic. Oral Glucose Tolerance Test was negative for gestational diabetes at week 24. She developed pre-eclampsia at week 35, and delivered a healthy girl at 39 weeks by spontaneous vaginal delivery. Blood pressure normalised after delivery and acromegaly symptoms remain under control. She is now off Hydrocortisone and is awaiting pituitary MRI once she has finished breastfeeding.
Conclusion
The growth hormone of placental origin gradually replaces the pituitary hormoneduring pregnancy. As a result, the IGF-1 declines during early pregnancy to increase later. The available experience regarding pregnancy in acromegaly is scant. The majority of the available data suggests that acromegaly remains stable during pregnancy, but the patients are at increased risk of gestational diabetes and hypertension. Hence, the management of these patients should be based on a multidisciplinary approach.

DOI: 10.1530/endoabs.65.P314

P315

The spectrum of testosterone levels in males with functioning gonadotroph adenomas: report of three cases

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Introduction
Functioning gonadotroph adenomas (FGAs) are very rare tumours secreting biologically active gonadotropins. In males, typically, FSH levels are elevated, whereas LH and testosterone are variable. Herein, we present three males with elevated, normal or low testosterone at diagnosis.
Cases
Case 1:42-year-old man with two-year history of visual impairment. Bitemporal hemianopia was confirmed. Imaging showed macroadenoma compressing optic chiasm. He had increased gonadotropins [FSH:88.3 IU/l (1.5–12.4), LH:26.2 IU/l (1.7–8.6)], increased testosterone [82.4 nmol/l (7–27)], normal SHBG [24.8 nmol/l (14.5–48.4)], hyperprolactinaemia, ACTH/ TSH deficiency. He did not report manifestations related with high testosterone but he had polycythaemia. Pituitary surgery was performed; pathology: adenoma with focal positivity for FSH and diffuse positivity for LH. Haemoglobin normalised post-operatively.
Case 2
39-year-old man with a few months' history of headaches and bitemporal hemianopia. Pituitary macroadenoma with chiasmal compression was found. He had increased FSH [45 IU/l (1.5–12.4)], low LH [1.1 IU/l (1.7–8.6)], normal testosterone [8.1 nmol/l (7–27)], normal SHBG (20.6 nmol/l) and hyperprolactinaemia. Pituitary surgery was performed; pathology: adenoma with mild focal FSH and LH expression.

Case 3
25-year-old man with 6-months history of visual deterioration. Left temporal hemianopia was confirmed. Imaging revealed macroadenoma distorting optic nerve. He had increased FSH [49.3 IU/l (2–11)], normal LH [1.3 IU/l (1–8)], low testosterone [4.7 nmol/l (7–27)], normal SHBG (24.8 nmol/l), hyperprolactinaemia, ACTH deficiency. Bilateral testicular enlargement was noted. Pituitary surgery was performed; pathology: adenoma with scattered FSH positivity.
Discussion/conclusions
Our cases highlight the wide spectrum of LH and testosterone concentrations in men with FGAs, mainly depending on hypersecretion of intact, biologically active LH and potential mass effects to normal gland. Co-secretion of intact FSH and LH is extremely rare and distinct clinical manifestations of high testosterone have not been, as yet, described in these patients.

DOI: 10.1530/endoabs.65.P315

P316

Hypopituitarism and patterns of hormonal replacement in an endocrinology clinic

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Introduction
Hypopituitarism refers to deficiency of one or more of the pituitary hormones. Hypopituitarism is often partial, thus replacement is individualized. Hormonal replacement improves quality of life in these patients.
Objective
To describe the demographic characteristics and patterns of hormonal replacement in patients with hypopituitarism attending the Endocrinology clinic of a tertiary hospital in Lagos, Nigeria.
Methods
We reviewed charts of patients with hypopituitarism attending the Endocrinology clinic of LUTH over a two year period. Information obtained from the charts included sex, age, aetiology of hypopituitarism and replacement therapy. Results were presented as averages and percentages.
Results
There were 22 patients, 12(55%) males and 10(45%) females. Mean age was 43 ± 11.85 years. 18(81.8%) had macroadenomas; 4(18.2%) microadenomas. Majority (16) of the patients with macroadenoma had undergone adenectomy, compared with 1 among those with microadenoma. Of the 22, 19(86.4%) were on hormonal therapy. The most frequently replaced hormone was Cortisol (14 patients); 12 on oral hydrocortisone, average dose 15 mg daily and 2 on prednisolone tablets, 5 mg daily. Hyperprolactinaemia occurred in 8 patients, 7 were on Tabs Cabergoline, average doses 0.25–0.5 mg twice weekly; 1 was on Tabs Bromocriptine. Thyroxine replacement was required in 6 patients, average dose 50 mcg daily. 2 patients required Desmopressin replacement. Only 1 male was on replacement with human chorionic gonadotropin. Overall, 11 (50%) required replacement with ≥ 2 hormones.
Conclusion
Majority of patients reviewed had previous adenectomy, underscoring necessity of endocrine assessment, post-surgery. Hormone replacement is usually life-long. Cortisol was the most frequently replaced. It appears there is a gap in screening for and replacing growth hormone in the clinic.
Keywords
Hypopituitarism, Hormone replacement therapy, Lagos, Nigeria

DOI: 10.1530/endoabs.65.P316

P317

Severe hyponatraemia in hospitalised patients – an endocrine problem?

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Background
Hyponatraemia is the most frequent electrolyte disturbance in hospitalised patients and is associated with increased morbidity and mortality as well as increased expenditure. Hyponatraemia is a common reason for referral to Endocrinology in the hospital setting however hyponatraemia has a variety of causes many of which do not come under the remit of 'Endocrinology'.
Aim
To determine the aetiology of severe hyponatraemia in hospital inpatients.
Methodology
Identification of all adult hospital inpatients with a sodium < 120 mmol/l in a 6 month period. Retrospective review of hospital records to determine aetiology of hyponatraemia.
Results
Two thirds of patients had more than one cause identified for their hyponatraemia. Of those with a single cause implicated the most common aetiology was drug-induced, mainly due to diuretics, antidepressants and proton pump inhibitors. Other common causes were malignancy, GI salt loss, dehydration and major organ failure. Adrenal insufficiency was seen only rarely and diagnosis was missed on more than one occasion. Syndrome of inappropriate ADH release (SIADH), seen infrequently, was mainly secondary to intra-cranial disease, malignancy, drugs or post-operatively. Most patients with malignancy associated SIADH had small cell lung cancer. The majority of other patients with hyponatremia and malignancy had alternative causes for hyponatraemia such as GI salt loss or hypovolaemia induced non-osmotic ADH release.
Discussion
Adrenal insufficiency and SIADH are infrequent causes of severe hyponatraemia in hospital inpatients. Hyponatraemia is more frequently seen in hypervolaemic states such as cirrhosis, congestive cardiac failure and end stage renal failure and hypovolaemic states such as dehydration, increased GI losses or over-diuresis. Common to many of these causes is a finding of hypotension and intra-vascular volume depletion which raises the possibility that hyponatraemia for many hospital inpatients is due to physiological and appropriate non-osmotic ADH release and thus is still an 'Endocrine' pathophysiology.

DOI: 10.1530/endoabs.65.P317

P318

Giant functional gonadotroph adenoma – case report

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A 49 year old male, known to suffer from hypertension, was bein investigated for recurrent occipital headaches. An MR Brain showed a 2.4 cm $\times$ 2.8 cm $\times$ 4.2 cm sellar mass with suprasellar extension, optic chiasm compression, infrasellar extension with erosion into the sphenoidal sinus, lateral extension into the left sided cavernous sinus and further extension through the cavernous sinus into the parietal lobe. The tumour contained some cystic areas and moderately enhanced with contrast. Pituitary function tests results showed: FSH 17.3 U/l (0.1–11), LH: 15.1 U/l (0.8–7.6), Testosterone 7 nmol/l (4.4–26.5) whilst thyroid function tests, cortisol, GH, IGF1 and prolactin were normal. The patient complained of bilateral gynaecomastia, testicular swelling and tenderness, mild lethargy and occasional nausea in the mornings. He denied visual disturbances. An ultrasound testes confirmed testicular enlargement with a right testicular volume of 21 ml and left testicular volume of 29 ml. He underwent transsphenoidal surgery for removal of the giant macroadenoma in September 2018. Histology showed a pituitary adenoma with strong diffuse LH and patchy FSH expression. Ki67 proliferative index was low (less than 3%). Post operatively FSH was 8 U/l, LH 4.7 U/l, Testosterone 4.4 nmol/l. The rest of his pituitary function tests were normal. Gynaecomastia and testicular symptoms significantly improved post operatively. His post-operative MR scan showed a small residual tumour mainly in the left cavernous sinus.
Discussion
Functional gonadotropin secreting adenomas are a rare entity with only few published cases in middle aged males. They are difficult to diagnose as hormonal secretion is erratic. They rarely cause a clinical syndrome. Excess FSH secretion results in testicular enlargement due to the increase in length of the seminiferous tubules. LH and testosterone levels can be low, normal or high. First line treatment is surgical resection of the adenoma. Regular clinical, biochemical and radiological follow up must be ensured.

DOI: 10.1530/endoabs.65.P318

P319

Panhypopituitarism secondary to hypothalamic involvement in Isolated Langerhans cell Histiocytosis

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A 68-year-old male presented with fatigue and acute onset polyuria and polydipsia. There was no history of headaches, visual symptoms, previous cranial radiations, chemotherapy or CNS infections. Investigations revealed normal fasting glucose, urea, creatinine, liver functions and electrolytes including calcium. Further workup including pituitary profile, paired osmolalities and water deprivation test confirmed hypopituitarism and cranial diabetes insipidus (Table 1). The underlying aetiology remained unclear as initial MRI Pituitary; Iron studies and CT chest/abdomen/pelvis were unremarkable. He was started on desmopressin and hormone replacements with improvement in his symptoms. His 1-year follow-up MRI pituitary was also unremarkable and remained asymptomatic until 18 months post initial diagnosis, when he developed aggressive behaviour and confusion, prompting MRI brain which showed a large midline suprasellar lesion in the region of hypothalamus. Repeat CT chest/abdomen/pelvis did not reveal any metastatic disease. Endoscopic biopsy of hypothalamic lesion confirmed Langerhans cell Histiocytosis on histology. He received 4 cycles of Cladibrine with associated regression of lesion in MRI but no improvement in cognitive function. He eventually succumbed to chest sepsis during his last hospitalization. This case highlights a rare case of isolated presence of Langerhans cell histiocytosis in hypothalamic region presenting with adult onset central diabetes insipidus, eventually leading to panhypoituitarism. Retrospective review of images showed that a very small hypothalamic lesion may have been overlooked on his follow-up scan at 1 year. Increased vigilance is therefore required when evaluating imaging with focus on hypothalamic region in addition to pituitary gland.

Table 1

TSH	1.97 miu/l	(0.38–5.33)
FT4	5.0 pmol/l	(7.0–16)
GH	0.1 mg/l	(0–2.8)
IGF-1	11.6 nmol/l	(5.6–25.4)
LH	0.2 iu/l	(1.2–8.6)
FSH	2.0 iu/l	(1.3–19.3)
Testosterone	<0.4 nmol/	(10–35)
Prolactin	1562 mu	(0–300)
ACE	120 u/l	(8–52)
Synacthen Test	0 h 24030 min 466	
serum sodium	147 mmol/l	
urine osmolality	151 mmol/l	
serum osmolality	297 mmol/l	

DOI: 10.1530/endoabs.65.P319

P320

Sheehan's syndrome in a sickle cell disease patient

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Background

Sheehan's syndrome (SS) is rarely encountered in developed countries due to advanced obstetric care but it is still frequent and a major threat to women in developing nations. Anaemia among other risk factors may increase the risk of Sheehan's syndrome.

Case report

36 year old woman, known sickle cell disease (SCD) patient with previous history of stroke in childhood, presented to the heamatologists on account of generalized body weakness and body pain of 3 weeks duration. While on admission, she was noticed to be having recurrent hypoglycemia. She had history of postpartum hemorrhage 7 years prior to presentation. Since then; there was history of failure to lactate, amenorrhea. She developed cold intolerance, slowness and hair loss few months afterwards. Admitting blood glucose was 10 mg/dl and blood pressure was 80/60 mmHg. She had hyponatremia (Na 128.1 mmol/l), 0800 h cortisol – 89.11 mmol/l(240–618), FSH – 5.72 IU/l, Prolactin – 1.22 ng/ml (3.3–26.7), TSH 1.703 mIU/l(0.380–5.330), FT4 0.129 pmol/l (7.2–16.4), FT3 0.001 pmol/l (3.8–6.0). Growth Hormone was <0.05 ng/ml. Cranial MRI and other hormonal profiles could not be done due to gross financial constraint. She was commenced on Intravenous fluid 5% Dextrose saline, IV hydrocortisone 100 mg 6 hourly, Levothyroxine 62.5 mcg dly. She was discharged home when stable on Tab Prednisolone 40 mg dly, Tab Levothyroxine 125 mcg on alternate days and has attended 2 outpatients follow up visits afterwards.

Discussion

Vessel occlusion and ischemia associated with SCD increases the risk of developing SS in addition to massive heamorrhage occuring during or after delivery leading to necrosis of the pituitary gland.

Conclusion

Sheehan's syndrome can be life threatening if not recognised. Early diagnosis and treatment with lifelong hormone replacement is important to reduce associated morbidity and mortality.

Keywords

Sheehan's syndrome, hypopituitarism, lactation failure, *postpartum* heamorrhage.

DOI: 10.1530/endoabs.65.P320

P321

A suprasellar germ cell tumour presenting with cranial diabetes insipidus

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A 30-year-old female presented to her general practitioner with a three-month history of fatigue, visual disturbance, polydipsia and dizziness. She was treated for iron deficiency anaemia, but re-presented two-months later with new-onset headache and worsening visual disturbance. Previously, she had childhood leukaemia, treated in Brazil with no cranial irradiation. On examination there was left eye loss of light/dark perception and right temporal vision loss. She was referred to our centre for further investigation. Blood tests revealed a sodium 158 mmol/l, urea 3.5 mmol/l, serum osmolality (calculated) 325 mOsm/kg and urine specific gravity 1.010. The patient was thirsty and drinking around 6 l/day. MRI head confirmed the presence of a large sellar mass with suprasellar extension, compression of the optic chiasm and hypothalamus and a similar second lesion. Pituitary function tests demonstrated raised serum prolactin (1729 mU/l, macroprolactin negative), morning cortisol 301 nmol/l and secondary hypothyroidism (free T4 7.7 pmol/l, TSH 0.33 mU/l). The patient started prednisolone 5 mg daily and subsequently 50 (g levothyroxine; she also started nasal DDAVP two sprays daily. Her serum hCG and AFP were normal, but an elevated CSF hCG (16 IU/l, normal <2) indicated a diagnosis of intracranial germ cell tumour. She was started on emergency etoposide/cisplatin (EP) chemotherapy followed by EP/OMB (vincristine, methotrexate, bleomycin) chemotherapy and intrathecal methotrexate. Three days later her visual perimetry had normalised and repeat imaging demonstrated a marked decrease in the suprasellar mass. Intracranial germ cell tumours can present with cranial diabetes insipidus (DI) as a result of compression of or invasion into the pituitary stalk. This tumour is an important differential in a young person and the case illustrates the need to assess CSF tumour markers when the serum values of hCG and/or AFP are normal.

DOI: 10.1530/endoabs.65.P321

P322

Pituitary incidentalomas: are we getting it right?

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Background
With advances in radiological technology, the detection of incidentally discovered pituitary abnormalities is increasing, 90% being secondary to pituitary adenomas. Patient morbidity increases when these lesions are large enough to cause hormone insufficiency or visual field defects, highlighting the importance of appropriate management.
Aim
To evaluate management of patients with pituitary incidentaloma in accordance with national guidelines at Lincoln County Hospital.
Methods
A guideline on management of pituitary incidentaloma was identified within 'The Journal of Endocrinology & Metabolism.' A retrospective data collection was obtained for 50 service users attending endocrinology clinics with pituitary incidentaloma from 2014 to 2019.
Results
At initial clinic presentation, 100% of patients underwent full history and examination and 90% (45/50) had clinical & laboratory evaluation for hormone hypersecretion and hypopituitarism. 92% (46/50) had MRI evaluation of the lesion. 34% (17/50) of these patients had a lesion abutting the optic chiasm on MRI, of which 71% (12/17) had visual field assessment within initial consultation. At follow up, MRI imaging was repeated at 6 months in 46% (19/41) of macroadenomas and at 12 months in 44% (4/9) of microadenomas. Visual field re-evaluation for chiasmal compressive lesions at 6 months was 41% (7/17) and 53% (9/17) at 12 months. Repeat biochemistry at 6 months was 63% (26/41) and 73% (30/41) at 12 months. Repeat MRI following symptomatic progression was 100%.
Conclusion
Visual field assessment is an important predictor of morbidity in pituitary incidentaloma and these results highlight that 29% of patients didn't have this assessed at initial evaluation. A proforma has been introduced within the endocrinology clinic to allow concurrent visual field assessment by ophthalmology during initial consultation. This project shall be re-audited in 1 year, with conformance to guidelines and patient satisfaction being used as outcomes of re-evaluation.

DOI: 10.1530/endoabs.65.P322

P323

Testosterone replacement exacerbating hyperprolactinaemia in a male patient with macroprolactinoma: A rare complication

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Hypogonadism persisting in males with macroprolactinoma requires exogenous testosterone replacement therapy but this may cause secondary elevations of prolactin. We present a case of a 44 year old gentleman who was diagnosed with macroprolactinoma after being investigated for 'abnormal thyroid function tests' with a low T4 and a normal TSH. He reported a few years' history of increasing weight gain, lethargy, generalised aches and pains, occasional headaches and low libido. TFTs suggestive of central hypothyroidism led to a diagnosis of macroprolactinoma (prolactin 131 000 IU/ml) with secondary hypothyroidism and hypogonadism. MRI pituitary confirmed a large macroadenoma with suprasellar extension causing displacement of the optic chiasm. He was started on cabergoline 250 mcg weekly up titrated to 500 mcg three times a week gradually with reduction in prolactin levels from 131 000 IU/ml o 12 566 IU/ml . A repeat MRI at 3 months showed reduction in the size of the pituitary lesion. He was then started on testosterone replacement (testogel). However, it was noted that his prolactin levels, which were previously responding well to cabergoline, became less responsive despite increasing the dose. He was taken off testosterone due to risk of testosterone converting to oestradiol and exacerbating hyperprolactinaemia. Cabergoline was further increased to 500 mcg five times a week and prolactin levels began to decrease. On reintroducing testosterone gel at that point led to the increase in prolactin levels again. Therefore it was stopped and was later changed to restandol (oral testosterone undecanoate) and cabergoline was further increased 500 mcg once daily. His most recent prolactin levels were 3892 IU/ml and were falling gradually. This case highlights the rare side effect of testosterone replacement leading to the worsening of hyperprolactinaemia in a male patient. Therefore, close monitoring is needed. The use of non-aromatizable androgens may be indicated in such patients.

DOI: 10.1530/endoabs.65.P323

P324

Prevalence of peripheral neuropathy, hyponatraemia and hypotension in patients admitted to hospital following a fall

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Background
Falls are a significant health problem and major burden on healthcare services. Falls are typically associated with ageing-related frailty, but diabetic peripheral neuropathy, postural hypotension and hyponatraemia are recognised risk factors for falling that might be independent of ageing-related factors. We undertook a study to assess the prevalence of these independent risk factors in patients admitted to hospital following a fall.
Methods
This study ($n=102$, 72 females, mean age 77.7 years) included a retrospective sample (RS) of 78 patients and prospective sample (PS) of 24 patients who presented to a district general hospital in the UK following a fall. Paper and electronic notes for all patients were analysed and the prospective patients were assessed for peripheral neuropathy.
Results
Of the102 patients none were assessed for peripheral neuropathy on admission despite a diabetes prevalence of 23%. In the PS group, 11 patients were identified (using touch the toe test and 10 g monofilament) as having peripheral neuropathy ($n=5$ with diabetes). Less than 10% of patients were assessed for postural hypotension despite 24% reporting associated symptoms. Hyponatraemia was identified in 36%.
Conclusion
This study has identified that after admission to hospital following a fall screening for some key risk factors is not routinely performed. From the PS, prevalence of peripheral neuropathy was 46%. Patients experiencing a fall need to be screened for postural hypotension and peripheral neuropathy, with quick bedside tests available. Hyponatraemia is common in elderly patients and needs greater attention in the community setting. Correctly identifying the presence of risk factors following a fall allows clinicians to make adjustments to a patient's care and reduce the risk of further falls.

DOI: 10.1530/endoabs.65.P324

P325

Non anorectic functional amenorrhea in young women

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Introduction
Functional amenorhea can appear due to chemical, emotional of physical chronic stress. It is particular pathology with special issues regagring long therm body sustaiment after the occurence of menses cessation. Material comprise 39 young women, with ages between 17 and 34, (mean age of 24.55 ± 6.09 years), 11 adolescents and 28 adult women, with secondary amenorrhea induced by weight loss, there were addressed to our Endocrine Unit, starting January 2014. Inclusion criteria: spontaneous menarche, regular menses prior to the amenorrhea episode, recent history of weight lost, no hormonal preparation used recently. Exclusion criteria: other central or peripheral causes of secondary amenorheea.
Method
We performed at baseline, and every 2 months in the following 12 months hormonal assays: FSH, LH, estradiol, progesterone, PRL, TSH, Ft4, anti TPO Ab., serum cortisol, midnight salivary cortisol, creatin, GFR, TGP, TGO. Intervention: supplemental therapy with analogues of natural estradiol.

Results
The weight loss responsible for secondary amenorrhea was smaller in adolescents than in adult women: 6.8 ± 1.21 kg vs. 33.5 ± 6.1 kg. The mean BMI was lower in adolescents (20.67 ± 2.18 kg/m^{2}sc) than in adult women (24.11 ± 3.9 kg/m^{2}sc). The mean weight loss was 6.5 ± 1.3 kg in adolescents, but 23.4 ± 4.8 kg in adult women. The degree of central suppression was similar: LH 1.15 ± 0.27 mUI/ml, in adolescents, vs. 1.28 ± 0.11 mUI/ml, in adult women $P = 0.67$. Gonadostat disinhibition appeared sooner in weight loos (9.5 ± 2.1 months) compared with a mean of 21.2 ± 4.5 months in stress induced amenorrhea, both in young women and in adolescents.
Conclusion
The vulnerability of gonadostat is higher in adolescents, but the recovery of the function apeeras after a modest weight. Stress induced amenorhea is more resilient to recovery.

DOI: 10.1530/endoabs.65.P325

P326

A rare pituitary tumour mimicking an adenoma – spindle cell oncocytoma

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Spindle cell oncocytoma (SCO) is a rare nonfunctioning neoplasm of the anterior pituitary gland .This tumour is often misdiagnosed as pituitary adenoma or pituitcytoma due to it's location and symptoms. Such tumours are highly vascular radiologically and histologically. We report a 54 year old gentleman who was found to have pituitary adenoma on CT head performed after a fall. Subsequent Pituitary MRI showed 25 × 18 mm pituitary macroadenoma with optic chiasm compression without cavernous sinus invasion. Biochemically it was non-functioning . Visual field assessment showed loss of colour vision in the left eye and a bitemporal visual field defect. He underwent transsphenoidal surgery and had an uncomplicated recovery. Histology results confirmed the diagnosis of spindle cell oncocytoma on immunohistochemistry and electron microscopy. Post transsphenoidal surgery patient developed partial anterior hypopituitarism and was commenced on levothyroxine, testosterone and hydrocortisone. Literature search shows that these tumours are rare and long term follow up is required as these tumours tend to reoccur. One case reported of malignant pituitary spindle cell oncocytoma requiring three surgeries and radiotherapy showing they can have potential to be malignant.

DOI: 10.1530/endoabs.65.P326

P327

Normocytic anaemia and fatigue can have unifying endocrine cause: Think outside the box: Think hypopituitarism: Think growth hormone

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35y woman presented to haematology with normocytic anaemia and extreme fatigue. Had borderline vitamin B12, but im hydroxocobalamin did not improve Hb. A trial of iv iron was also ineffective. Bone marrow biopsy showed hypocellular bone marrow with suppressed erythropoiesis. In the absence of underlying cause, commenced prednisolone with significant improvement in Hb from 117 to 134 g/l and she felt better. Prednisolone was continued at 5 mg od. Fatigue, musculoskeletal symptoms, joint aches and paraesthesia persisted. Rheumatologist diagnosed fibromyalgia and did 0900 h cortisol, which was borderline. Short synacthen test was suboptimal (basal 143 nmol/l, 30 min: 273 nmol/l), but ACTH- 19, IGF-1- 30 nmol/l, LH-7.9 iu/l, FSH-5.7 iu/l, prolactin- 167 mu/l, TSH-1.34 mu/l, T4-11.5 pmol/l and pituitary MRI were normal. Her adrenal antibodies, renin were normal. Suboptimal SST was initially thought to be due to iatrogenic suppression by prior exogenous prednisolone. She continued Hydrocortisone alone for approximately 12 months with only partial symptomatic improvement. Anaemia persisted (Hb-107–118 g/l). Despite normal IGF-1, we proceeded to insulin stress test. This demonstrated severe GH and cortisol deficiency with peak cortisol 59 nmol/l and GH 0. 09 mcg/l. Diagnosis of idiopathic partial hypopituitarism was made, and GH was commenced with dose titration to 0.4 mg a day. At six months post GH initiation, she reported significant improvement in her symptoms and her Hb has normalised to 121 g/l.
Discussion
Hypopituitarism should be considered in normocytic normochromic anaemia in the absence of an alternative explanation. IGF-1 could be normal in severe GH deficiency and if Hb is not improving with hydrocortisone alone, dynamic stress test should be performed to exclude concurrent GH deficiency as GH also affects erythropoiesis. It might take up to six months on steroids + GH to normalise anaemia.

DOI: 10.1530/endoabs.65.P327

P328

Normocytic anaemia and fatigue can have unifying endocrine diagnosis: Think outside the box: Think Hypopituitarism: Think growth hormone

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35y woman presented to haematology with normocytic anaemia and extreme fatigue. Had borderline vitamin B12, but im hydroxocobalamin did not improve Hb. A trial of iv iron was also ineffective. Bone marrow biopsy showed hypocellular bone marrow with suppressed erythropoiesis. In the absence of underlying cause, commenced prednisolone with significant improvement in Hb from 117 to 134 g/l and she felt better. Prednisolone was continued at 5 mg od. Fatigue, musculoskeletal symptoms, joint aches and paraesthesia persisted. Rheumatologist diagnosed fibromyalgia and did 0900 h cortisol, which was borderline. Short synacthen test was suboptimal (basal 143 nmol/l, 30 min:273 - nmol/l), but ACTH- 19, IGF-1- 30 nmol/l, LH-7.9 iu/l, FSH-5.7 iu/l, prolactin-167 mu/l, TSH-1.34 mu/l, T4-11.5 pmol/l and pituitary MRI were normal. Her adrenal antibodies, renin were normal. Suboptimal SST was initially thought to be due to iatrogenic suppression by prior exogenous prednisolone. She continued Hydrocortisone alone for approximately 12 months with only partial symptomatic improvement. Anaemia persisted (Hb-107–118 g/l). Despite normal IGF-1, we proceeded to insulin stress test. This demonstrated severe GH and cortisol deficiency with peak cortisol 59 nmol/l and GH 0. 09 (g/l. Diagnosis of idiopathic partial hypopituitarism was made, and GH was commenced with dose titration to 0.4 mg a day. At six months post GH initiation, she reported significant improvement in her symptoms and her Hb has normalised to 121 g/l.
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DOI: 10.1530/endoabs.65.P328

P329

CNS lymphoma masquerading as pituitary macroadenoma

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Introduction
Non-Hodgkin lymphoma (NHL) involving the hypothalamus and pituitary gland is rare. Central nervous system involvement by NHL may be either as a primary tumour or from systemic lymphoma. We report an interesting case of aggressive central nervous system (CNS) lymphoma presenting as pituitary macroadenoma.
Case report
A 67-year-old Caucasian woman presented with sudden onset of left eye ptosis and diplopia. Examination showed left third nerve palsy and visual field assessment revealed that she had bilateral inferior nasal defect. Pituitary function tests demonstrated hypocortisolaemia, secondary hypothyroidism and hypogonadotropic hypogonadism and she was commenced on Hydrocortisone and Levothyroxine. Magnetic resonance imaging (MRI) revealed pituitary macroadenoma measuring 14×12×11 mm with suprasellar extension. She underwent a CT angiogram that was normal. She had a history of diffuse large B-cell lymphoma in complete remission for more than 2 years. A repeat pituitary MRI within a month revealed that the lesion progressed to involve the hypothalamus and the optic tract. She underwent a biopsy of hypothalamic lesion that confirmed diffuse large B-cell CNS lymphoma. She was commenced on chemo-immunotherapy. Following second cycle of chemotherapy she developed transient diabetes insipidus (DI) requiring replacement with Desmopressin. Despite three cycles of chemotherapy, her intracranial disease progressed rapidly to involve the ventricles, posterior nasopharynx and possibly small nodes above and below the diaphragm. Subsequently the multidisciplinary Haematology team decided to discontinue active treatment and advised palliative care support.
Discussion
Sudden onset of ophthalmoplegia, headaches and DI in patients over 50 years should raise a suspicion of lymphoma or metastasis to the pituitary gland. NHL is a common lymphoma of the CNS. DI is the common presentation as the posterior lobe of pituitary receives blood supply directly from systemic circulation. In initial stages, MRI might not differentiate the aetiology. Hence biopsy is the gold standard to make accurate diagnosis.

DOI: 10.1530/endoabs.65.P329

P330

An unusual case of orthostatic hypertension likely secondary to dysautonomia

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Introduction
Orthostatic hypertension (OHT) is a phenomenon which may represent increased cardiovascular risk and is less well recognized compared to orthostatic hypotension.
Case
A 65 year old gentleman presented with symptoms of lethargy and episodic shaking. He has a history of treated prostate cancer and was not on any regular medications. He noticed consistently elevated blood pressure on standing during home monitoring. His lying BP was 142/82 and standing BP was 184/114 in clinic and other systems exam was unremarkable. Plasma metanephrines and a Head up tilt test were organized, results awaited. As he had consistent and significant increase in postural BP, he was commenced on Doxazosin at night.
Discussion
OHT has been variably defined in literature. Although usually asymptomatic, non-vertiginous dizziness can be a presenting symptom. OHT was prevalent in 28% (in contrast to 16% for orthostatic hypotension) in the PARTAGE study of elderly institutionalized population but previous reports in community individuals have varied between 1 and 11%. Alpha-adrenergic sympathetic hyperactivity has been the suggested mechanism. Patients with OHT have been noted to have elevated norepinephrine levels and peripheral vascular sensitivity. Whilst OHT has been considered to be a marker of cardiovascular frailty and has been associated with masked hypertension, consistent evidence linking OHT and adverse outcomes is lacking. The Japan Morning Surge 1 Study showed that Doxazosin suppressed orthostatic BP increase and reduced urine albumin excretion.
Conclusion
Assessing people for postural blood pressure may identify this group of individuals with potentially increased CV risk and allow early intervention. However, the evidence for specific treatment of OHT is still lacking.

DOI: 10.1530/endoabs.65.P330

P331

I would love to remove my head= pituitary apoplexy

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Pituitary apoplexy is a medical emergency and rapid replacement with hydrocortisone may be lifesaving. Apoplexy is often the first manifestation of an underlying pituitary adenoma. We report a case of apoplexy in a patient with an undiagnosed pituitary adenoma who presented with sudden onset headache and subtle neurology in the form of minor left ptosis. A 64-year-old male with a background of hypertension, asthma-COPD overlap syndrome and bronchiectasis presented to A&E with acute sudden onset headache, vomiting and dizziness. He denied any visual symptoms. Examination revealed very mild left sided ptosis with no other neurological deficit. Urgent non-contrast CT head showed no acute haemorrhage or infarction.Due to the persistent symptoms and unexplained partial ptosis, an out of hours CT angiogram was requested. This showed a 4(5 mm aneurysm of the distal MCA, enlargement of the pituitary fossa and a possible pituitary mass. Urgent ophthalmology review confirmed left partial ptosis and bitemporal hemianopia with possible left ischemic optic neuropathy. Hormonal profile showed random cortisol of 144 nmol/l (whilst on prednisolone 30 mg/d for COPD), normal thyroid function tests and prolactin. Testosterone was low at 5.9 nmol/l. Pituitary MRI with contrast done on the following day showed an enlarged pituitary measuring 2.1×2.2 cm. Heterogenous signal was noted on T1 weighted images with central low signal but peripheral high signal suggestive of blood products, in addition to the MCA aneurysm. He was transferred to the local neurosurgical centre and underwent transsphenoidal pituitary surgery. Postoperative visual field assessment showed full recovery. He was started on hydrocortisone replacement. The MCA aneurysm is being managed conservatively.
Learning points
1-Pituitray apoplexy often occurs in undiagnosed pituitary tumours.
2-Subtle neurology in association with other symptoms should trigger further evaluation.
3-Dual pathology can co-exist, such as aneurysm and apoplexy.
4-Multidisciplinary approach is crucial.

DOI: 10.1530/endoabs.65.P331

P332

Recurrent pregnancy induced pituitary apoplexy in a patient with a macro-prolactinoma

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A 23-year-old woman was referred with light periods and subfertility with a raised prolactin (1175 miu/l). Remaining pituitary function tests were normal. As she was now pregnant, investigations were postponed until post-pregnancy. *Post-partum* prolactin was 1823 miu/l and MRI pituitary demonstrated a 13.5 mm pituitary macroadenoma. Cabergoline was commenced but stopped due to a further pregnancy. At 22 weeks gestation she experienced left visual field loss. MRI showed subacute haemorrhage within the pituitary. Prolactin 1673 miu/l, cortisol 354 nmol/l, thyroid function normal. The remainder of the pregnancy was uneventful. MRI *post-partum* showed reduced size of the pituitary lesion. There was no indication for surgery and she was restarted on cabergoline. During her third pregnancy an MRI scan was arranged due to constriction of the visual fields showing new haemorrhage. Prolactin was 2351 miu/l. Remaining pituitary function tests were normal. She was commenced on hydrocortisone. The remainder of her pregnancy was uneventful. Five days *post-partum* she presented with severe headache. MRI showed no evidence of fresh haemorrhage and a reduction in size of the pituitary lesion. She restarted cabergoline with good response; prolactin 25 miu/l with significant reduction in lesion size (4.5 mm).

Her prolactin rose to 2055 miu/l when cabergoline was discontinued and it was restarted. During a further pregnancy she presented with severe headaches at 27 weeks. MRI showed a significantly enlarged pituitary gland with evidence of an acute haemorrhage into the gland. There was no derangement in pituitary function. She successfully completed her pregnancy and continues on oral hydrocortisone. Pituitary apoplexy is a rare but potentially life threatening condition. There is increased risk in pregnancy due to the physiological enlargement of the pituitary gland. To our knowledge this is the first documented case of recurrent pregnancy induced pituitary apoplexy. This case raises questions over the optimum management of pregnancy induced apoplexy.

DOI: 10.1530/endoabs.65.P332

P333

A rare case of metastatic insulinoma

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A 24 year old gentleman presented following an episode where he became 'sleepy' and disorientated whilst driving and had to pull over. He was confused and lethargic and paramedics found blood glucose of 2 mmol/l. He gave a 3-week history of extreme lethargy, nausea, epigastric discomfort, blurring of vision and constant hunger. He denied recent weight changes and had no significant past medical/family history. Biochemical evaluation was as follows; Laboratory glucose 1.4 mmol/l, C-peptide 404 pmol/l, insulin 7.7 mU/l, Cortisol 430 nmol/l, Ca19–9 6 IU/ml, TSH 0.57 mU/l, IGF-1 25 nmol/l. MRI pancreas was performed which revealed multiple metastases throughout the liver but no primary lesion identified due to severe motion artefact. Subsequently a full staging CT CAP was performed which revealed pancreatic duct dilatation with a possible obstructing primary lesion at the pancreatic body/tail junction, with liver metastasis. The radiologist confirmed possible metastatic insulinoma or neuroendocrine tumour and this was discussed at the upper GI MDT meeting. Meanwhile, he was commenced on diazoxide at a dose of 100 mg TDS with good response. He proceeded to have a liver biopsy and Octreotide scan. The histology from liver biopsy revealed grade 2 neuroendocrine tumour, metastasize to the liver in keeping with a pancreatic primary neuroendocrine tumour (clinically insulin producing) with Ki67 of 13%. Octreotide scan revealed highly avid segment 7 liver lesions but interestingly other lesions including the pancreatic lesion were octreotide negative indicating variation in disease, hence PET scan was organised. The initial management is chemotherapy with Streptozocin and Capecitabine with surgery/embolization as required to treat residual disease.

Conclusion

Malignant insulinoma is rare accounting for only 5–12% of cases of insulinoma with median survival of approximately 2 years. This case highlights the challenges of insulinoma diagnosis and localisation and the role of first line medical therapy as opposed to surgery in those with unresectable metastasis.

DOI: 10.1530/endoabs.65.P333

P334

Co-secreting TSH and growth hormone pituitary adenoma

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The co-existence of thyrotropin (TSH) and growth hormone (GH) secreting pituitary adenoma is exceedingly rare. Less than 15 cases having been reported.

Case report

A 75 years' old man presented with new-onset atrial fibrillation. He had high FT4 with normal TSH. His ultrasound scan of the neck showed a solitary nodule. He had ablation twice and was started on bisoprolol and anticoagulant. He had an MRI scan for headaches and this showed a pituitary macroadenoma. He had high IGF-1. His oral glucose tolerance showed failure of GH suppression. His FT4 was persistently high with normal TSH and he had high subunits. This suggested the diagnosis of TSH and GH secreting pituitary adenoma.

Discussion

TSH-secreting pituitary adenomas are rare and not uncommonly, they co-secrete other pituitary hormones including growth hormones. Somatotrophs and lactotrophs share common transcription factors with thyrotrophs. TSH-secreting adenomas are benign but 60% of them are locally invasive. TSH-secreting pituitary adenomas typically present with either symptom of tumor growth like headache or visual field disturbance or symptoms of hyperthyroidism. Thyroid nodules are common in patients with TSHomas. In patients with TSH-secreting pituitary adenomas, the majority will need only surgery and radiation. The medical treatment used to normalize TSH and FT4 levels is somatostatin analogs. This is effective in about 90% of patients with TSH secreting pituitary adenomas TSHoma should be differentiated from resistance to the thyroid (RTH). The main difference between TSHoma and RTH is the presence of signs and symptoms of hyperthyroidism in patients with TSHoma, absence of family history, normal thyroid hormone levels in family members, and the presence of an elevated glycoprotein α-subunit in patients with a pituitary tumor.

Reference

LH Adams and D Adams. A case of a co-secreting TSH and growth hormone pituitary adenoma presenting with a thyroid nodule. EDM Case Reports 2018.

DOI: 10.1530/endoabs.65.P334

Nursing Practice

P335

The role of microbiological cultures in managing diabetic foot osteomyelitis

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Background and aims

Diabetic foot osteomyelitis (DFO) is a well-recognised complication and a risk factor for lower limb loss. Its effective treatment can reduce the risk of minor and major amputations. Our aim was to compare the yield in cultures from the proximal and distal segments of bone excised intraoperatively as part of the management of DFO and the impact on antibiotic choice and duration.

Materials and methods

Patients attending the diabetic foot service at the Queen Elizabeth Hospital Birmingham between 2013–2018 with a confirmed diagnosis of osteomyelitis on bone culture results, with a proximal and distal bone segment samples were retrospectively selected from electronic hospital records. Microbiological data was reviewed on these samples collected intraoperatively and true pathogens were identified and studied against antimicrobial choice and duration of prescribing.

Results

During the study period, a total of 47 forefoot amputation cases were studied. There were 83% males and the mean age of the patients was 64 years (range 43–94 years). In 89% of cases, definite or possible pathogens were isolated from the deep tissues cultured. Definite pathogens (Gram positive cocci: Staphylococcus aureus, Group B Streptococcus, Group G Streptococcus and Streptococcus anginosus) were identified in 32% cases; in 73% of these, definite pathogens were grown in both the proximal and distal bone segments. In 60% of these cases antimicrobial prescription was in-line with the microbiologists' recommendations. 89% of the patients had 12 months post-operative amputation free survival.

Conclusion

It is challenging to correctly estimate whether intraoperatively clear surgical margins have been achieved when resecting infected bone. Patients may therefore need a prolonged course of culture-aligned antimicrobials to achieve complete cure. In our centre when cultures from proximal bone samples are negative, the duration of the antibiotics courses can be reduced in 27% of patients.

DOI: 10.1530/endoabs.65.P335

P336

Effectiveness of a nurse-led adrenal incidentaloma (AI) clinic at the University Hospital of Wales, Cardiff

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Background

In December 2017, a Nurse-Led AI clinic was introduced at University Hospital of Wales, Cardiff for the evaluation and follow-up of these patients. The clinic pathway was based upon the 2016 European Society for Endocrinology (ESE) guidelines on the management of adrenal incidentalomas.

Aim
To evaluate the effectiveness of this new service and the cost-saving benefit.
Methods
Electronic and paper-based patient records were evaluated from December 2017 to April 2019. Total numbers assessed, referral times, time to discharge, numbers needing consultant follow-up and estimated cost savings were evaluated. Cost-savings were calculated in comparison with the previous management of AI.
Results
A total of 68 patients were seen over the 17-month period. The mean time from the initial CT prompting referral to being assessed in the nurse-led clinic was 3.6 months. A total of 30 patients were discharged from the service based upon satisfactory radiological and biochemistry evaluation. A further 12 were diverted into a consultant-led clinic due to biochemistry findings ($n=9$), radiological findings ($n=2$) or being transferred to a different Health Board ($n=1$). A further 26 patients are currently under ongoing assessment with the service (awaiting biochemistry results only ($n=5$), waiting repeat CT only ($n=2$) and repeat CT and biochemistry ($n=19$)). Therefore, 30/42 (71%) patients having completed the nurse-led evaluation have been discharged from the service. 18/30 (60%) were seen only in one clinic and 12/30 (40%) seen twice before discharge. The mean time from the first contact with the nurse and discharge from the service was 5.7 months. It is estimated that this service has saved a total of around £40 000 so far (2 CT scans (each £200), 4 annual biochemistry assessments (each £72.83) and 4 annual appointments (each £160) for 30 patients).
Conclusions
A nurse-led service is an efficient and cost-saving method to manage AI in secondary care setting.

DOI: 10.1530/endoabs.65.P336

P337

A pituitary problem in pregnancy

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A 29 year old woman, 21 weeks pregnant with no previous medical history was admitted with 5 days blurred vision in the left eye and headaches, worse in the morning and lying flat. Three weeks previously she had been treated with antibiotics for a group A strep infection. An urgent MRI suggested pituitary apoplexy with left optic chiasm nerve compression. IV hydrocortisone 100 mg TDS was commenced reduced to 20 mg TDS. Investigations showed TSH 0.2 mu/l, FT4 10.4 pmol/l, FT3 2.6 pmol/l. Prolactin concentration was normal for pregnancy. Thyroxine 50 mcg/day was commenced. Subsequently she developed mild diabetes insipidus (DI) managed with oral desmopressin (DDAVP). In view of progressive deterioration of her visual fields, urgent transphenoidal decompression of the chiasm was performed. Following surgery vision improved substantially, but DI persisted, requiring high doses of DDAVP. Histology suggested the most likely diagnosis was autoimmune lymphocytic hypophysitis. Follow up was in the interdisciplinary maternal medicine clinic with monitoring of electrolytes. She was induced at 38 weeks. Fluid balance, serum electrolytes and urine osmolality were monitored closely during labour and delivery, the DDAVP doses adjusted as indicated. A healthy baby was delivered. Post-delivery short synacthen test was normal and oral hydrocortisone stopped. DI also resolved four months postpartum and DDAVP was discontinued. Currently she remains on thyroxine. Throughout this stressful experience the patient was supported by the Pituitary Nurse Specialist for advice, guidance and psychological support. This report describes the unusual occurrence of pituitary apoplexy complicated by DI occurring during pregnancy, and its successful management throughout remaining pregnancy and labour. Lymphocytic hypophysitis is a rare condition where the pituitary gland is infiltrated by lymphocytes, with pituitary enlargement and impaired function. It often occurs in women in late pregnancy or the postpartum period. The exact cause is unknown, but maybe autoimmune related.

DOI: 10.1530/endoabs.65.P337

P338

Cortisol alert dog: Improving patient outcomes?

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Introduction/Aim
In Addison's disease, patient-self maintenance of adequate cortisol levels is essential. Optimising cortisol control is challenging and well documented. Traditional management aims to ensure adequate daily cortisol levels, management of stressful situations/acute illness, avoiding over replacement. Alert dogs are currently used to support patients with hypoglycaemia unawareness. Recent reported international studies of alert dogs in primary and secondary ACTH deficiency is limited. These studies have produced some evidence to suggest that dogs can be trained to detect low cortisol. Further investigation is essential to establish the importance of the use of alert dogs. This case study seeks to establish how an alert dog can have an impact on optimising ACTH deficiency and improve patient outcomes.
Methods
We studied one patient and her dog, which is being trained using Pavlovian conditioning to alert the patient to low cortisol levels. To ensure that subjective issues could be discussed, the patient was interviewed using a mix of open and rating scale questions. The previous results of dynamic testing were compared with those collected during the investigation with the alert dog.
Results
The Hydrocortisone Day Curve (HCDC) results collected during the study demonstrate that the patient requirement for hydrocortisone is less. In the previous HCDC requirement was 30 mg (15-10-5) and subsequent HCDC demonstrated a reduction to 25 mg (10-10-5). The dog alerted the patient each time when her cortisol levels went below 180 nmol/l. The questionnaire showed multiple benefits of having an alert dog. This includes enhanced levels of independence, confidence and well-being.
Conclusion/Discussion
Preliminary data suggests that an alert dog can successfully be trained to detect low cortisol levels. Patient's ability to manage steroid requirements is optimized; quality of life demonstrates significant improvement. Further investigation includes single-centre study or multi-centre. There are limitations to this study.

DOI: 10.1530/endoabs.65.P338

P339

Use of a holistic needs assessment questionnaire to inform 'late effects' clinic appointments for childhood cancer survivors

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The number of childhood cancer survivors is ever increasing and as this population continues to grow, the long term physical and psychological impact of having cancer treatment in childhood becomes ever more apparent. Childhood cancer survivors are moving into adulthood with significant health needs secondary to their cancer treatment. Acknowledging and addressing these needs is crucial in supporting them on their continued health journey. Patients attending the 'late effects' clinics for childhood cancer survivors were asked to complete a holistic needs assessment questionnaire prior to their clinic appointment, in an attempt to identify their concerns and ensure the appointment was fulfilling the patients' needs as well as the clinicians. The questionnaire listed nineteen potential topics for discussion. Patients were then invited to bring the completed form into clinic where the health needs they had identified could be discussed further. 35 patients completed the assessment. Most frequently reported health needs were concentration (40%), fatigue (40%), fertility (37%), weight (37%) and psychological (31%). Body Mass Index (BMI) of patients who identified weight as a health need revealed 38% to be underweight, 31% overweight, 23% obese and 8% severely obese. The brain tumour and bone marrow transplant survivors were reporting these problems most frequently, who were all treated with cranial irradiation, and will all require lifelong endocrine follow-up. Use of the holistic needs assessment questionnaire enabled patients to ensure that their concerns were discussed in clinic, often directing the discussion away from traditional 'medical' priorities. When needs could not be met by the clinic team, resources could be provided (for example, information leaflets about managing fatigue) and onward referrals made (for example, for neuropsychological assessments or to specialist fertility services). The results also illustrate the complex multi-faceted on-going needs of childhood cancer survivors, particularly those who have been treated with cranial irradiation.

DOI: 10.1530/endoabs.65.P339

P340

A simple tool to assess the self-care management knowledge and skill needs of people with adrenal insufficiency (AI) before their adrenal education

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We adapted holistic needs assessment tool used in oncology setting to create a simple tool to assess the learning need of people with adrenal insufficiency. This simple tool consists of 17 items and it allows endocrine nurse educators to obtain a quick assessment on the self-care management knowledge and skill of people with adrenal insufficiency before embarking on adrenal education.
The tool 17 items are:
Understanding of adrenal insufficiency
Recognising adrenal crisis
Awareness of support groups (for emotional and psychological needs)
Oral medication dosing
Hydrocortisone knowledge
Hydrocortisone injection
Effects of over replacement
Effects of under replacement
Sick Days Rules
Long term effects of replacement
Alcohol
Exercise & activity
Traveling
Relationship and intimacy
Planning pregnancy
Education course available.
We also collected over 30+ data from cohorts attended our clinics and ADSHG members attending our adrenal education training. These data consist of both people with adrenal insufficiency and their friends and carers. This also allow endocrine nurse educator to tailor their education priorities as well as planning the subsequent follow up training required for people with AI.
Conclusion
A simple tool to use in clinic setting to obtain a quick assessment on the learning needs of people with AI and their carer.

DOI: 10.1530/endoabs.65.P340

P341

One-week biochemical investigations in Cushing's disease – from the endocrine specialist nurse perspective

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Background
Cushing's disease is the most common cause of endogenous Cushing's syndrome in adults, affecting females>males (ratio 3:1). In suspected cases, careful clinical assessment is required to ascertain a pre-test probability. This is followed by robust biochemical testing, which guides further management.
One-week test protocol
Congruent biochemical tests are conducted over a one-week period in an outpatient setting. Patients attend on day 1, bringing two 24 h urine collections for measurement of urinary free cortisol (UFC), and two late-night salivary cortisol (LNSC) samples, collected during the preceding 48 h. On day-1, a serum cortisol day profile is performed with LNSC to assess the diurnal rhythm. Plasma adrenocorticotrophic hormone (ACTH) is also checked at 0900 h. On the second day, at 0900 h, anterior pituitary function tests (including repeat ACTH) are performed, followed by the commencement of a low dose dexamethasone suppression test (Table 1). Patients receive instructions on the appropriate method/technique for performing each test. Patients symptoms, medications and basic observations are recorded.
Key
ACTH, adrenocorticotrophic hormone; CDC, cortisol day curve; LDDST, low dose dexamethasone suppression test; LNSC, late-night salivary cortisol; UFC; urinary free cortisol.
Illustrative case
An 18-year-old lady with mild learning-difficulty presented with clinical features of Cushing's syndrome. Outpatient investigation (with close instructions regarding test methodology and sample collection techniques) was undertaken. Results confirmed pituitary-dependent Cushing's. Transsphenoidal adenomectomy was successful in rendering the patient in complete remission (hydrocortisone dependent) with no other pituitary deficits.

Table 1 One-week outpatient Cushing's investigation protocol

Patient's home	Endocrine unit (outpatient visits)				
Sat	Sun	Mon	Tue	Wed	Thu
UFC	UFC	CDC, ACTH	0900 h pituitary profile, ACTH	Continue LDDST	0900 h cortisol
LNSC	LNSC	LNSC	LDDST		

Conclusion
Accurate sample collection, timing and labelling is a crucial step in the correct interpretation of Cushing's investigations. Focussed one-week testing allows better instruction delivery by the endocrine nurse.

DOI: 10.1530/endoabs.65.P341

P342

More than just tea and cake. The benefit of patient to patient peer support

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Introduction
Acromegaly is caused by excessive growth hormone production and elevated IGF-1 levels. Annual incidence rates are reported to be between 0.2 and 1.1 cases/100 000 people, with a prevalence of 2.8–13.7 cases/100 000 people. Small numbers make it difficult to differentiate any differences between sex. A recent increase in the number of females diagnosed with acromegaly at our centre, voiced a need for peer and psychological support. It is known that acromegaly patients suffer from decrease quality of life and increase in anxiety and depression. Peer support has been documented to be of benefit for patients with the same diagnosis.
Method
Evidence of a successful peer support meeting at another endocrine centre motivated us to follow a similar format. Invites were sent to ten female acromegalic patients at our centre inviting them to afternoon tea, organised by two endocrine clinical nurse specialists (CNS). An informal agenda; purpose, ground rules, icebreaker and what brought them to the meeting was set, lasting two hours. Evaluation forms were completed at the end, requesting feedback and how to plan and improve future meetings.
Results
40% of those invited attend, two also brought a family member, 40% of those unable to attend wished to be included in future meetings, 20% declined. All of the attendees rated the meeting good to excellent. They enjoyed; the informality of the meeting, being able to meet others with the same condition, and felt comfortable to share stories. A group text chat was set up between attendees, allowing continuation of communication. Recommendations: This meeting formed a catalyst for future meetings to be organised by patients with support as required from the endocrine CNS. Thereby, empowering patients and ensuring their identified needs continue to be met.

DOI: 10.1530/endoabs.65.P342

Reproductive Endocrinology and Biology

P343

Neuroendocrine control of puberty in primates: differential involvement of two distinct populations of GnRH neurons?

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Gonadotropin-releasing hormone (GnRH) neurons represent the primary neuroendocrine link between the brain and the reproductive system. Although

they play a key role in stimulating the release of LH and FSH from the anterior pituitary gland, the underlying mechanism by which they trigger the onset of puberty is unclear. To address this issue, RT-PCR, in situ hybridization histochemistry, and Affymetrix gene arrays were used to profile hypothalamic GnRH gene expression in prepubertal and adult rhesus macaques. Like humans, these primates express two molecular forms of GnRH (GnRH-I and GnRH-II), both of which are highly effective at stimulating gonadotropin release via the same GnRHR1 receptor but only *GnRH-II* showing increased expression in the presence of elevated estrogen concentrations (i.e., positive feedback). Overall, the hypothalamic expression levels of *GnRH-I and GnRHR1* were found to be no different between prepubertal and adult animals, despite marked differences in circulating sex-steroid hormone levels. In contrast, the hypothalamic expression level of *GnRH-II* was significantly higher in the adults. Therefore, although GnRH-I neurons are likely to play a fundamental role in re-initiating LH and FSH release at the end of the juvenile period, in humans and nonhuman primates, it is plausible that the GnRH-II neurons play a key role in maintaining elevated gonadotropin release during the later stages of pubertal development (i.e., at a time when the GnRH-I neurons are subjected to increased negative sex-steroid feedback from the maturing gonads).

DOI: 10.1530/endoabs.65.P343

P344

Defining the impact of paternal diet on testicular morphology and apoptosis

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While the association between maternal nutrition and female reproductive fitness and offspring health is well recognised, the role that paternal diet plays in shaping male reproductive health is relatively poorly understood. It is, however, well established that poor diet has adverse effects on sperm quality, which in turn have a negative impact on embryo development and offspring health. It is conceivable that behind any alterations to sperm quality, there are certain underlying changes in testicular morphology. Few studies, however, assess the impact of diet on testicular histology. Therefore, we fed C57BL6 male mice either a control normal protein diet (18% protein; NPD), isocaloric low protein diet (9% protein; LPD), or a low protein diet supplemented with methyl donors (MD-LPD) for at least 7 weeks. Testes were collected and processed for either morphological (histology) or gene expression (RT-qPCR) analysis. We observed that LPD-derived testes displayed significantly increased mean total seminiferous tubule area and epithelium relative to NPD and MD-LPD ($P<.02$). In contrast, increased tubule lumen area was observed in response to MD-LPD ($P=.02$). Analysis of gene expression patterns revealed that testicular expression of anti-apoptosis gene *Bcl2* (Apoptosis regulator Bcl-2) was increased in response to LPD and MD-LPD ($P<.05$), whereas the expression of the pro-apoptosis gene *Bax* (Apoptosis regulator BAX) was significantly decreased in the MD-LPD group ($P=.01$). Finally, we assessed testicular apoptosis using TUNEL staining. We observed that the level of apoptosis was significantly decreased in LPD when compared to NPD ($P=.014$). In addition, the supplementation of LPD with certain vitamins and minerals mitigated some of the changes to testicular morphology and apoptosis. This data provides further insight into testicular morphology and apoptosis in response to poor paternal diet and the possible underlying mechanisms taking place.

DOI: 10.1530/endoabs.65.P344

P345

Placental expression of progesterone receptor is down regulated in fructose-induced diabetic rats

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Maternal diabetes is known to impair placental function; however, its effect on placental expression of progesterone and oestrogen receptors has not been well documented. Fructose has been used to induce insulin resistance in animal models (Suga *et al.,* 2000). The study aimed to assess maternal serum levels of progesterone, oestriol, oestradiol; placental morphology and its expression of progesterone and oestrogens receptors in fructose-induced diabetic rats. Twelve female rats were randomly divided into two groups namely group 1; control rats fed with normal rat chow and group 2; treated rats fed a diet consisting of 25% fructose to induce type 2 diabetes mellitus. Hyperglycaemia and hyperinsulinemia were confirmed after 8 weeks of fructose feeding. Rats in both groups were mated and pregnancy confirmed. Blood samples were obtained and assessed for glucose, insulin, progesterone, oestriol and oestradiol levels. Placental tissues were isolated, weighed and fixed for morphological studies and the expression of oestrogens and progesterone receptors using immunohistochemical technique. Results showed that blood glucose, insulin and progesterone levels were significantly increased in the diabetic rats with no significant difference in oestriol and oestradiol levels. Placental weight, central thickness and diameter were increased; placental junctional zones were enlarged due to an increase in the number of glycogen and trophoblast giant cells in the diabetic placentae. Progesterone receptor expression was down regulated in the placentae of diabetic rats, while there was no significant difference in oestrogens receptor expression compared to the control placentae. Type 2 diabetes mellitus therefore increases progesterone levels, impairs placental morphology and down regulates placental progesterone receptor expression in pregnant rats.

Keywords
placenta, diabetes, pregnancy

Reference

Suga, A., Hirano, T., Kageyama, H. (2000). Effects of fructose and glucose on plasma leptin, insulin and insulin resistance in lean and VMH – lesioned obese rats. *American Journal of Physiology-Endocrinology and Metabolism,* 278(4): E677–E683.

DOI: 10.1530/endoabs.65.P345

P346

Islet adaptations to pregnancy: a role for Urocortin 2

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Previous studies have shown beneficial effects of the corticotropin releasing hormone (CRH) family, including the urocortins (UCN1, UCN2 and UCN3), on pancreatic islets and subsequent glucose homeostasis. However, the physiological relevance of this interaction is not currently understood. CRH and urocortins are also expressed by placenta, so this study investigated whether signalling through CRH receptor 1 or 2 (CRHR1/CRHR2) plays a role in the islet adaptation to pregnancy. Pregnant CD1 mice were chronically administered CRHR antagonists from gestational day 7 by subcutaneous osmotic minipumps. Intraperitoneal glucose tolerance and insulin tolerance tests were performed on gestational day 16 and 18 respectively. Plasma levels of CRH and urocortins were compared between pregnant and non-pregnant mice using ELISAs. Blocking total CRHR signalling during pregnancy resulted in impaired glucose tolerance, significantly 15 minutes post glucose (Control: 13.22 ± 1.08 vs. α-helical CRF_{9-41}: 16.83 ± 1.60 mmol/l; $P<0.05$; mean ± S.E.M.; $n=$ 8–19). Similarly, impaired glucose tolerance was observed in mice administered the CRHR2 antagonist; Antisauvagine-30 (Control: 13.22 ± 1.08 vs. Antisauvagine-30: 16.63 ± 1.60 mmol/l; $P<0.05$), but not in animals treated with the CRHR1 antagonist; Antalarmin hydrochloride (Control: 13.22 ± 1.08 vs. Antalarmin hydrochloride: 11.93 ± 1.30 mmol/l; $P>0.05$). Insulin sensitivity was unaffected by CRHR antagonists (AUC-0–60 min, control: 372 ± 23; Antisauvagine-30: 347 ± 20; Antalarmin hydrochloride: 368 ± 22; $P>0.5$; $n=7$–19). UCN2 was the only one of the CRH family to display an increase in levels during pregnancy (non-pregnant: 92.87 ± 8.33 vs. pregnant: 178.23 ± 37.46 pmol/l, $P<0.001$; $n=6$–8), whilst CRH, UCN1 and UCN3 levels were unchanged. Blocking CRHR2 signalling during pregnancy impairs glucose tolerance, suggesting an endogenous CRHR2 ligand improves glucose tolerance during pregnancy. This ligand is most likely UCN2 because of the increased levels observed in pregnant mice, suggesting an important and novel role for placental UCN2 in the islet adaptation to pregnancy.

DOI: 10.1530/endoabs.65.P346

P347

Vitamin D binding protein (DBP) is required for pro-invasion effects of vitamin D on placental trophoblastic cells

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The active form of vitamin D, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) is abundant in decidua but its role in placental development is unclear. We hypothesized that decidual $1,25(OH)_2D$ promotes placentation in early-pregnancy via actions on trophoblastic cell invasion. Using trophoblastic JEG3, BeWo and HTR8 cells we showed that $1,25(OH)_2D$ has no effect on trophoblastic cell proliferation and migration in plasticware culture. However, in Matrigel transwell cultures, $1,25(OH)_2D$ potently promoted trophoblastic cell invasion. Vitamin D system analysis showed complete absence of the nuclear vitamin D receptor (VDR) in plasticware culture of JEG3, BeWo and HTR8 cells, whilst TPC cells showed strong nuclear VDR and potent $1,25(OH)_2D$-mediated induction of VDR target genes such as *CYP24A1*. Conversely, on Matrigel, trophoblastic cells showed abundant expression of VDR, with stronger nuclear localization in the presence of $1,25(OH)_2D$, whilst TPC showed no VDR. Notably, all cells showed intracellular expression of the serum vitamin D binding protein (DBP) in Matrigel but not plastic culture. Intracellular expression of DBP appeared to be due to uptake of exogenous DBP, with serum-free cultures showing no intracellular DBP. Trophoblastic and TPC cells showed non-genomic response to $1,25(OH)_2D$ through induction and nuclear localization of phosphoERK1/2 (pERK1/2), and inhibition of ERK1/2 blocked DBP uptake and trophoblast Matrigel invasion. Likewise, low serum/low DBP culture dramatically suppressed trophoblastic matrix invasion. These data suggest VDR and DBP cooperate to promote decidual invasion by trophoblastic cells, with $1,25(OH)_2D$ enhancing cellular uptake of serum DBP by pERK-mediated signaling. We, therefore, propose that healthy placentation requires the actions of both $1,25(OH)_2D$ and its serum carrier protein, with maternal levels of DBP and its uptake by trophoblastic cells being a new important consideration in the overall impact of vitamin D on pregnancy success.

DOI: 10.1530/endoabs.65.P347

P348

Impact of a FSHR positive allosteric modulator on FSH glycosylation variant-dependent FSHR homomerisation and signal pathway activation

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The heterodimeric pituitary glycoprotein hormone, follicle-stimulating hormone (FSH) and its target G protein-coupled receptor (FSHR) are essential for reproduction. As an important drug target for IVF, the need for more effective treatment drives interest in understanding what modulates FSH/FSHR functions. In vivo, two predominant FSH glycosylation variants have been identified; partially glycosylated FSH (FSH21) has faster binding kinetics to the FSHR and is more potent at activating cAMP-dependent signal pathways, in comparison to fully glycosylated FSH (FSH24). An important mechanism of regulating GPCR function is the formation of dimers and oligomers. FSHR has been shown to self-associate, and our unpublished data suggests that the increased bioactivity of FSH21 may be mediated via dissociation of FSHR oligomers into dimers and monomers, with no effect of FSH24 observed. As FSH24 displays slower binding kinetics to FSHR, we aimed to determine the effect of Compound 2 (C2), a FSHR positive allosteric modulator on FSH glycoform receptor binding, FSHR oligomerisation and signal pathway activation. C2 increased both FSH21 and FSH24 receptor binding. In HEK293 cells transiently expressing FSHR, 30-min pre-treatment $+/-$ 1 μM C2, enhanced the concentrations-dependent effects of FSH21 on CREB phosphorylation. Moreover, co-treatment with C2 enhanced FSH24-dependent CREB activation at low concentrations but had no effect on FSH24-dependent CREB-P at concentrations of FSH24 >1 ng/ml. Super-resolution imaging via PD-PALM of FSHR homomers showed that C2 pre-treatment had no effect on the number of FSHR monomers and homomers observed. However, C2 pre-treatment caused rapid FSH24-dependent dissociation of FSHR homomers into monomers and lower order trimers. Interestingly, C2 had little effect on FSH21-dependent regulation of FSHR complexes. These data suggest that allosteric modulation of FSHR is a powerful tool for enhancing FSH-FSHR action, modulating signal strength, with potential as a novel therapeutic strategy for enhancing ovarian responses during IVF protocols.

DOI: 10.1530/endoabs.65.P348

P349

miR-1-3p and miR-133-3p are altered in maternal serum EVs and placenta in pregnancies complicated by gestational diabetes with large-for-gestational age babies

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Gestational diabetes (GDM) is a form of diabetes that is first diagnosed during pregnancy, complicating 8–24% of all pregnancies. Despite treatment, substantial numbers of babies are born large for gestational age (LGA), predisposing them to cardio-metabolic disease in adulthood. It is difficult to predict which pregnancies are most at risk. The study aimed to determine if circulating maternal serum small extracellular vesicle (sEV) miRNAs have the potential to predict altered fetal growth in mothers with GDM. Maternal serum samples were collected from women at the time of GDM diagnosis (26–28 weeks); placental tissue was collected at delivery and birth outcomes recorded. Serum sEVs were isolated and characterised through electron microscopy, nanoparticle tracking analysis, and Western blotting for EV enriched proteins TSG101 and HSP70. miRNA QPCR arrays were performed and several miRNAs were altered in sEVs in women that subsequently delivered LGA ($n=7$) compared to appropriately grown for gestational age (AGA) babies ($n=7$). This includes reduced miR-145-5p and increased levels of 'angiomiRs' miR-1-3p, miR-133a-3p and miR-499a-3p, which are all key regulators of vascular development. GDM is associated with altered placenta vascular development, and our previous studies have shown that sEVs can be transported from the maternal circulation into the placenta where they can influence cellular processes. To determine whether altered sEV miRNAs have the potential to contribute to changes in placental vascularisation, we assessed levels of altered sEV miRNAs in placenta. QPCR analysis revealed that miR-1-3p, miR-133a-3p, miR-145-5p and miR-499a-3p were all present in the placenta at term, and that miR-1-3p and miR-133a-3p were reduced in placenta from GDM pregnancies with LGA ($n=11$) compared to AGA ($n=11$; $P<0.05$). In conclusion, angiomiRs could have predictive value for aberrant fetal growth in cases of GDM, and miR-1-3p and miR-133a-3p may also contribute to altered placental vascular development.

DOI: 10.1530/endoabs.65.P349

P350

Gonadotrophin rise following the kisspeptin analogue (MVT-602) is increased in women with hypothalamic amenorrhoea compared to healthy women

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Introduction
Hypothalamic amenorrhoea (HA) is a condition characterised by reduced GnRH pulsatility and is a common cause of anovulatory subfertility. Kisspeptin is an endogenous neuropeptide that regulates hypothalamic GnRH function. Hypothalamic kisspeptin expression is reduced, and kisspeptin receptor expression is increased, in a rodent model of HA. The kisspeptin analogue MVT-602 has a 3-4-fold longer half-life than native kisspeptin-54 ($t_{1/2}$ 0.5 h). We investigated the endocrine response to MVT-602 in women with HA to evaluate its potential as a treatment for anovulatory subfertility.

Methods
A previous dose-finding study in healthy women determined that no further increase in gonadotrophin response was observed at doses of MVT-602 greater than 0.03 nmol/kg. We therefore compared the response to MVT-602 0.03 nmol/kg in healthy women during the follicular phase ($n=9$) to women with HA ($n=6$). Reproductive hormone levels were measured every 30 mins for 24 h and at 48 h. Intervention groups were compared by Mann–Whitney *U* test.
Results
Median (IQR) maximal rise in LH following MVT-602, was over three-fold greater in women with HA at 17.8 iU/l (7.4, 30.7) compared to healthy women at 5.6 iU/l (4.4, 9.6; $P=0.02$). Median (IQR) maximal rise in FSH was over seven-fold greater in women with HA at 10.6 iU/l (5.0, 13.6) in comparison to healthy women at 1.4 iU/l (0.4, 3.1; $P=0.001$). Oestradiol rise was also greater in women with HA at 547 pmol/l (373, 1218) than in healthy women at 371 pmol/l (118, 420; $P=0.03$). The first peak in LH also occurred sooner in women with HA at 6.0 h (5.9, 6.9) when compared to healthy women at 21.0 h (10, 22.5; $P=0.01$).
Conclusion
In women with HA, the rise in gonadotrophins following the kisspeptin analogue, MVT-602, is more pronounced and occurs sooner than in healthy women. The augmented and sustained rise in oestradiol demonstrates the potential for MVT-602 to restore reproductive health in anovulatory women with HA.

DOI: 10.1530/endoabs.65.P350

P351

Igf2 regulates placental endocrine capacity in the mouse placenta

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Introduction
Abnormal fetal growth can cause perinatal morbidity and mortality. The placenta regulates materno-fetal nutrient transfer and secretes hormones with maternal physiological effects. In mice, global loss of insulin-like growth factor 2 (*Igf2*), a paternally-expressed imprinted gene, causes fetoplacental growth restriction in association with changes in placental transport and endocrine zone (Jz) formation. However, the role of *Igf2* in regulating placental endocrine function is unknown. We hypothesised that *Igf2* loss in the Jz (Jz-*Igf2*UE) would impair placental endocrine cell formation and hormone expression.
Methods
Heterozygous *Igf2Flox* males were mated with homozygous *TpbpaCre* female mice to generate litters of mixed genotype; 50:50 wildtype and Jz-*Igf2*UE. Fetal and placental weights were recorded on day 16 of pregnancy (term ~day 20.5), when the Jz is at its largest. Placentas were bisected. One half was fixed in paraformaldehyde for histological assessment. The Jz of the other half was isolated and snap frozen for qPCR analysis of *Igf2*, *Igf2* receptors, hormones and endocrine cell markers. Fetuses were sexed by *Sry* genotyping. Significant genotypic differences were assessed by *t*-test ($P<0.05$).
Results
Fetal and placental weights were unaltered with Jz-*Igf2*UE. However, Jz volumes of spongiotrophoblasts and glycogen cells were decreased in females with unaltered placental glycogen concentrations in both sexes. In both sexes, Jz-*Igf2*UE reduced Jz *Igf2* expression and increased the steroidogenic gene, *Cyp17a1*. In females, Jz-*Igf2*UE increased insulin receptor α (*Insra*) and *Tpbpa*, but decreased insulin receptor β (*Insrb*) and placental lactogen 2 (*Prl3b1*). In males, Jz-*Igf2*UE decreased the type 2 IGF receptor (*Igf2r*) and trended to reduce the glycogen cell marker (*Gjb3;* $P=0.07$).
Conclusions
Jz-*Igf2*UE alters the cellular composition and hormone expression of the placental Jz. However, the nature of these changes were dependent on fetal sex. Despite changes in placental endocrine phenotype with Jz-*Igf2*UE, fetal and placental weights were unchanged in a mixed litter.

DOI: 10.1530/endoabs.65.P351

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Oxytocin as a new target in treating ejaculatory disorders?

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Oxytocin was suggested to affect sperm volume and ejaculation. The most distal part of the epididymis stores the sperm until ejaculation and was therefore our main focus when investigating parts of the rat epididymis and vas deferens for local differences of the contractile responses to oxytocin in comparison to norepinephrine regarding their usability for targeted drug development. Single loops of the coiled epididymal duct from defined parts of the epididymis and the adjacent part of the vas deferens (DDpe) were observed using time lapse imaging and organ bath studies ($n\geq6$). Special interest was paid to the last segment of the epididymis (S19) and the DDpe which is where the sperm is stored before release during ejaculation. The effects in the rat adult tissue with sperm were compared to the effects in neonatal tissue without any sperm present. S19 and DDpe showed a significant response to oxytocin (0,5 μM) with the response to oxytocin being significantly greater than the one to norepinephrine (10 μM). However, oxytocin showed no significant effects throughout all the other (more proximal) parts of the epididymis, responsible for sperm maturation and transport. Interestingly the same experiments conducted in the neonatal tissue again showed no significant response to oxytocin throughout all the other parts of the epididymis and a significant response in S19 and DDpe but the response to norepinephrine was always greater than oxytocin. These insights in combination with other local and central effects of oxytocin agonists and antagonists found may result in new treatment options for a variety of ejaculation associated disorders (premature ejaculation, delayed ejaculation) or as a male contraceptive.

DOI: 10.1530/endoabs.65.P352

P353

Differential expression in granulosa-lutein (GL) cells from polycystic ovaries of genes implicated in assembly and modification of extracellular matrix (ECM)

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Introduction
Polycystic ovary syndrome (PCOS) is the commonest endocrine disorder in women and polycystic ovaries are characterized by excess ovarian stroma that has implications for disordered follicle development in PCOS. The factors contributing to proliferation and increased density of stroma remain unclear but local overproduction of androgens may be involved.
Aim
To examine differential expression of genes that regulate key proteins that comprise ECM and, in particular, ECM-modifying genes that are involved in collagen processing.
Methods
From our database of 450 differentially expressed genes in GL cells (RNAseq) from 12 women with and 12 without PCOS, we manually identified genes (PubMed) that regulate synthesis and processing of ECM proteins.
Results
We found significant differential gene expression of 7 structural ECM molecules. Three collagens were downregulated (*COL5A2*, *COL11A1* and *COL4A1,* a basal lamina protein, as was *FREM2*) and *FBLN7* (Fibulin7). Two ECM genes were upregulated (*COL21A1* and *LAMA3*). Importantly, 3 genes that post-translationally modify collagen were differentially expressed; *PLOD2*, *P4HA2 and LEPREL1,* as were *LOX,* which cross-links collagen, and *MIA3,* involved in collagen secretion. Two further genes involved in ECM remodelling, *MMP19* and *HPSE,* were upregulated. In a parallel study of effects of dihydrotestosterone on mouse ovarian follicles, we have found evidence for androgen regulation of *Coll11a1, Coll 4a1, Fbln7, Lama3, Plod2, HPSE* and *MMP19.*
Conclusion
Genes that are important for assembly and, especially, processing of ECM molecules are differentially expressed in GL cells from PCOS women. These changes are likely to contribute to altered structure and function of the stromal component of polycystic ovaries and highlight signalling pathways for further

investigation. There is evidence, from our animal studies, that some of these pathways are influenced by androgen signalling.

DOI: 10.1530/endoabs.65.P353

P354

Maternal cardiovascular risk and pregnancy outcomes in turner syndrome – new evidence supports current guidance

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Introduction

The risk of maternal death from aortic-dissection(AoD) during pregnancy/post-partum in TS is increased, due to TS-associated risk factors (bicuspid-aortic-valve (BAV), aortic-coarctation, aortic-dilatation, hypertension) and the increased cardiovascular strain of pregnancy itself. TS-guidelines advice against pregnancy in the presence of severe aortic-dilatation or moderate dilatation with AoD-risk factors; and after aortic surgery a high risk remains. However, few studies focus on cardiovascular outcomes in pregnant TS.

Methods

Retrospective study on 42 life-birth pregnancies among 25 TS women. Echocardiography/CMR pre-pregnancy($<$2y *pre-partum*) and post-pregnancy($<$2y *post-partum*) were collected. Measurements of sinuses of Valsalva (SoV) and ascending aorta(AA) were reviewed and adjusted for body-surface-area(ASI). AA-ASI$\geq$20 mm/m^2 defined moderately dilated aorta, $\geq$25 mm/m^2 severely dilatated. Change in diameter pre- and post-pregnancy were compared with the growth rate of 70 nulliparous-TS.

Results

Cardiac-status at preconception was evaluated in 11/25 women. 2/11 had AA-ASI$\geq$20 mm/m^2, respectively, with BAV and hypertension. 3/11 had BAV, with repaired aortic-coarctation in 2. 1/25 had a previous AA-replacement. 2/25 had twin pregnancies with oocyte-donation. Post-pregnancy SoV and AA were significantly increased compared with pre-pregnancy values. The annual aortic-diameter-growth pregnancy-related was higher vs. nulliparous women. Among the five women with pre-exisiting AoD-risk factors, aortic-growth was higher, although not significant. There were no peri/post-pregnancy AoD.

Time between cardiac-scans 3.6 (1.6–4) y	Pre-pregnancy	Post-pregnancy	Pregnant	Nulliparous	
SoV, mm	28.0 $\pm$ 2.6	29.5 $\pm$ 3.8			$<$0.000
AA, mm	25.9 $\pm$ 3.7	28.1 $\pm$ 5.5			$<$0.000
SoV growth-rate, mm/y			0.53 $\pm$ 0.68	0.13 $\pm$ 0.59	0.044
AA growth-rate, mm/y			0.61 $\pm$ 0.67	0.22 $\pm$ 0.83	0.142

Conclusions

This is the first study evaluating pre-pregnancy and post-pregnancy cardiovascular status in TS and suggest that aortic diameters increase during pregnancy, especially in women with pre-pregnancy AoD-risk factors. These data support the current guidelines regarding careful cardiovascular evaluation prior to any pregnancy and close pre and post-pregnancy monitoring.

DOI: 10.1530/endoabs.65.P354

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Identifying placental hormones regulating maternal physiology during pregnancy – potential diagnostic and treatment markers for pregnancy complications

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Pregnancy is characterised by profound changes in maternal physiology. For instance, there are changes in the metabolic, cardiovascular, immune and renal systems of the mother which enable her to support fetal nutrient supply and growth. These changes are signalled in part by the production of protein hormones by the placenta (Napso *et al*., 2018). Failures in maternal adaptation and placental function lead to pregnancy complications such as abnormal birth weight and gestational diabetes. However, we lack information on the identity of hormones secreted by the placenta that mediate the changes in maternal physiology. This study aimed to identify the protein hormones expressed by endocrine cells in the mouse placenta. Primary cell cultures of the whole placenta from mouse dams on day 16 of gestation were established (term = 20 days). Proteins in the conditioned media (serum-free) at 48 h of culture were identified by LC–MS. In parallel, endocrine cells were sorted from whole placentas of mice on day 16 of pregnancy using fluorescence-activated cell sorting. Peptides expressed by placental endocrine cell isolates were identified by LC–MS. Protein IDs were converted to gene lists using accession ID. Gene lists were overlaid with published mouse and human placental RNA-seq data ($n=3$ and $n=6$, respectively). We identified a total of 1195 proteins in mouse placental endocrine cell isolates and secretomes (85% overlap between two types of samples), of which 34% are known to be secreted. Gene ontology identified that placental endocrine cell proteins have proposed roles in metabolic regulation, immune modulation, signalling and growth. Most proteins/genes have homologues expressed by the human placenta and several are reported to be dysregulated in women with pregnancy complications like abnormal birthweight and gestational diabetes. Work is currently underway to assess whether secreted placental proteins could serve as diagnostic indicators for human pregnancy complications.

DOI: 10.1530/endoabs.65.P355

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Are all kisspeptins equal? The effect of kisspeptin 10 and kisspeptin 54 on kisspeptin-mediated signalling

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Kisspeptin (Kp) and its receptor (KISS1R) are essential for reproduction, with dysfunction in their activities leading to reproductive disorders, such as precocious puberty and hypogonadotrophic hypogonadism. Kp is synthesised and secreted within specialist nuclei of the hypothalamus, modulating the HPG axis. Kp is a 54 amino acid peptide, which can undergo proteolytic cleavage into smaller peptides, including Kp10, which retain biological activities. However, little is known about the functional and biological significance of these differential Kp peptide variants. Kp/KISS1R are expressed in a range of tissues, with tissue specific variation in the Kp peptide variant locally produced, suggesting that the Kp54 proteolytic cleavage may provide a means of modulating the tissue-specific functionalities of the Kp/KISS1R system. Our study therefore aimed to assess the effects of Kp10 and Kp54 on KISS1R-mediated downstream signalling in different cell types. We first utilised HEK293 cells transiently expressing the KISS1R. As an indicator of Gαq activation, calcium mobilisation via Fluo4-direct dye and confocal microscopy showed differences in maximum responses to Kp10 and Kp54, with Kp10 more potent than Kp54 ($P<0.001$, $n=8$–16). Time-dependent analysis of Kp10 and Kp54 showed a similar acute 5 min-activation of P-ERK, which was sustained for 60 min. Although not significant, a trend for enhanced Kp10-dependent ERK activation was observed at all time points. To explore tissue-dependent effects of Kp10 and Kp54, we switched to GnRH neuronal cell line (FCBN4 cells). A phosphokinase array revealed differential regulation of 10 phosphokinases by Kp10 and Kp54. Time-dependent analysis of two phosphokinase hits via Western blotting showed a trend for increased Kp54-dependent P-ERK at 10 min in comparison to Kp10. Analysis of Kp10 and Kp-54-dependent P-CREB also suggested differences in time course experiments. Our findings suggest differences in the biopotencies of Kp10 and Kp54, with biological significance remaining to be determined.

DOI: 10.1530/endoabs.65.P356

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Deciphering the effects of testosterone on FSH glycosylation variant-dependent ERK/MAPK activation

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The heterodimeric glycoprotein hormone, follicle stimulating hormone (FSH) and its receptor (FSHR) are vital for reproductive function, driving ovarian function via follicular recruitment, selection and development. FSH exists as two predominant glycoforms in females; partially glycosylated (FSH21) and fully glycosylated (FSH24), based on differing glycosylation patterns of the β subunit. The FSH glycoforms have different bioactivities, with FSH21 displaying a higher binding affinity for FSHR, shorter circulating half-life and increased potency of Gas-dependent signalling pathways, than FSH24. FSH21 and FSH24 are co-secreted, with the ratio of FSH21:FSH24 changing with age, with FSH21 predominant in women of reproductive prime, and FSH24 predominant in menopausal/post-menopausal women. Little is known about how the ovarian steroid hormone environment regulates FSH21 and FSH24 functions. The aim of this study was to determine the effects of testosterone on FSH/FSHR-dependent signal pathway activation. The cell model was the human granulosa cell line (KGN) cells, that endogenously express FSHR. KGN cells were pre-treated $\pm$500 nM testosterone for 48 h, and subsequently stimulated for 15 min with either FSH21 or FSH24. In the absence of testosterone pre-treatment, FSH21 increased ERK-phosphorylation in a concentration-dependent manner. The response was biphasic, with 0.01 nM FSH21 resulting in a 2.0-fold increase in ERK phosphorylation, and maximum response of 2.7-fold increase with 1 nM FSH21, and decreasing thereafter. Surprisingly, pre-treatment with testosterone attenuated FSH21 dependent ERK phosphorylation. Suggesting possible pathway cross-talk to regulate FSHR signalling. In the absence of testosterone, FSH24 also stimulated ERK-phosphorylation, but was less potent than FSH21. Pre-treatment with testosterone ablated FSH24-dependent ERK phosphorylation. These data suggest that the endocrine microenvironment plays an important role in regulating FSH/FSHR signalling, with the ovarian functional consequences to be determined.

DOI: 10.1530/endoabs.65.P357

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Effects of the endocrine disrupting chemical bisphenol A (BPA) in human placentation *in vitro*

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Endocrine disrupting chemicals (EDCs) are environmental chemicals/toxicants that humans and wildlife are exposed to and which interfere with the action of hormones. Bisphenol A (BPA) is classified as an EDC with xenoestrogenic activity and is recognized by the WHO as a chemical with potentially potent effects on humans throughout different phases of development. A significant knowledge gap still exists regarding the complete spectrum of BPA-induced effects on human physiology, particularly on the placenta. As such, the present studies examined the effects of physiologically relevant doses BPA *in vitro*, using BeWo cells a well-characterised human placental cell line model. Treatment of BeWo cells with 3 nM BPA, induced cell proliferation and increased phosphorylation of p38. When treating BeWo cells with ER antagonists, there was a significant decrease in proliferation over 24 h when cells were treated with G15 (a GPR30 antagonist) and a moderate decrease when treated with the ERα antagonist ICI 182 780. Furthermore, microarray analysis identified 1195 genes that were differentially regulated in 3 nM BPA-treated BeWo cells. Most upregulated genes include: cytoplasmatic polyadenylation element-binding protein 1 (CPEB1), Myosin Light Chain 3 (MYL3), Caveolin-1 (CAV1), Calsyntenin-3 (CLSTN3), Hydroxycarboxylic acid receptor 3 (HCAR3), Serpin B9 (SERPINB9), Alanine-glyoxylate aminotransferase 2 (AGXT2), Transmembrane protein 45B (TMEM45B) and Eukaryotic translation initiation factor 4E type 2 (EIF4E2). Top 10 pathways associated with differentially expressed genes using Enrichr software, included leptin and insulin signalling, differentiation of white and brown adipocyte and integrin-mediated cell adhesion. Collectively our data provide a new insight of functions of BPA at placental level and provide a potential link with metabolic changes that can impact on the developing fetus.

DOI: 10.1530/endoabs.65.P358

P359

Normosmic idiopathic hypogonadotrophic hypogonadism in two homozygous siblings with a familial novel GnRH1 gene mutation

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Introduction

Idiopathic hypogonadotrophic hypogonadism (IHH) with normal sense of smell is a complex and rare disease entity characterised by insufficient gonadotropin releasing hormone (GnRH) neuronal action on an intact hypothalamo–pituitary–gonadal axis. IHH has an incidence of 1–10 in 100 000 live births with a variable mode of inheritance and five-fold male predominance. Gene mutations have been discovered of which 10–40% of the familial cases are due to GnRH receptor mutation. We report a case of normosmic IHH due to a novel familial GnRH1 mutation.

Case

A 17-year-old male presented with delayed puberty. He was born three months premature by caesarean section. His parents were second cousins in a consanguineous marriage. The patient had normal growth with no learning difficulties. On examination he had small testes, micropenis and bilateral gynaecomastia. He had normal sense of smell. Pituitary profile showed low luteinising hormone ($<$1 U/l), follicle stimulation hormone ($<$1 U/l), testosterone (0.3 nmol/l) and androstenedione ($<$1.1) levels with normal prolactin, vitamin D and thyroid hormone levels. MRI scan of the pituitary was normal. Bone density scan revealed osteopenia. Chromosomal analysis revealed 46XY phenotype and genetic analysis revealed a homozygous variant in GnRH1 [c.119_122dupGAGA, p.(Asp41Glufs*8)]. The patient's sister, born with a cleft palate, was also found to be homozygous for the GnRH1 mutation. She is currently on hormone replacement therapy. Genetic testing of the both parents revealed heterozygous carriers for the same mutation. The patient continues to show progressive sexual development on hormone replacement therapy.

Discussion

Mutations in the GnRH1 gene are a rare cause of IHH. Family members can be affected with variable penetrance of the gene mutation. We present a new gene mutation, which most likely has an autosomal recessive pattern of inheritance. Early diagnosis is essential to mitigate psychological distress and physical sequelae, and to restore fertility in affected individuals.

DOI: 10.1530/endoabs.65.P359

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Pirimiphos-methyl modulates the timing of puberty and ovarian functions in female rats

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Developmental exposure to endocrine-disrupting compounds may adversely affect female reproductive physiology. The present study investigated the effect of Pirimiphos-methyl (PM), an organophosphate pesticide, widely used to protect crops and grains against pests, on puberty onset in female rats. Female weanling rats were orally treated with 20 mg/kg and 40 mg/kg of PM for ten consecutive days from postnatal day 22 to 31. Following vagina opening and attainment of estrus and dioestrus phases of the estrous cycle, rats were sacrificed by cervical

dislocation. Blood was collected via cardiac puncture to determine serum level of progesterone, oestradiol (E_2) and anti-mullerian hormone (AMH) using enzyme-linked immunosorbent assay. Ovaries were collected to determine follicular count as well as the expression of gonadotropin-releasing hormone (GnRH) receptor by immunohistochemistry. Exposure to 20 mg/kg of PM for 10 days advanced vaginal opening. Ovaries were undersized and showed decreased number of follicles in PM-treated rats. Serum levels of progesterone and AMH were reduced ($P<0.05$) by PM treatment while E_2 level was increased ($P<0.05$) when compared with control. The expression of ovarian GnRH receptor was significantly reduced following exposure to 20 mg/kg of PM. In conclusion, the present study showed that PM-induced puberty advancement is related to disturbance in the activity of the hypothalamic–pituitary–gonadal axis.

Keywords
pirimiphos-methyl, puberty, anti mullerian hormone, estrous, immuno-histochemistry.

DOI: 10.1530/endoabs.65.P360

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Options for childbearing and pregnancy outcomes in Turner syndrome

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Spontaneous pregnancy (SP) in TS is rare (4.8–7.6%). Oocyte-donation-*in-vitro*-fertilization (IVF-OD) and fertility-preservation increasingly offer the possibility of childbearing. Nevertheless, pregnancy is associated with an increased risk of complications. Adoption/surrogacy represents alternative parenting options.

Aim

To analyse parenting options and pregnancy outcomes inTS.

Methods

Data was collected in 154 TSwomen, median age 32y, including parenting options, method of conception and birth outcomes.

Results

21 (13.6%) had SP, 48% ≥one miscarriage; 35 newborns were delivered by 18 women. Age at first SP was 23.8y (15–31); 4 women had unwanted pregnancies. All women with SP had spontaneous menarche, 61.1% were mosaic 45,X/46,XX, 11.1% 45,X. SP-complications; 2 women developed preeclampsia, 2 gestational diabetes. 1/35 offspring had TS. Among women with no SP (136), 15.4% considered IVF-OD. 4 women were unable to proceed with IVF-OD: 2 aged>35y not eligible for funding, one increased BMI, one increased cardiac-risks. 14 women received 39 cycles, age at first IVF-OD was 31.2y; 7 delivered 9 newborns and 7 stopped trying after unsuccessful attempts/miscarriages. Despite guidelines recommending single embryo-transfer, 4 women received two embryo-transfer (2 recently outside UK due to lack of funding); 2 pairs of twins were delivered, 2 started with twin pregnancies, one resulting in the miscarriage of one and the other both twins. IVF-OD complications; 2 developed gestational diabetes. 3 considered adoption; one adopted, one with increased cardiac-risk has started the process, one withdrew (too intrusive) and is investigating surrogacy. One aged 17y had oocyte-cryopreservation with successful oocyte retrieval. Four were not interested in childbearing.

Conclusions

This is the first study focusing on fertility options in TS. We found a higher prevalence of SP compared to previous studies. IVF-OD was successful in half who attempted and we emphasize the importance of single embryo-transfer to avoid complications. Overall, pregnancy outcomes were good in both SP and IVF-OD.

DOI: 10.1530/endoabs.65.P361

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Placental GLUT9 expression is associated with altered fetal growth in pregnancies complicated with GDM

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Gestational Diabetes Mellitus (GDM) is associated with adverse outcomes, including large-for-gestational age (LGA) babies who are are at greater risk of developing cardiovascular and metabolic diseases in adulthood. The mechanisms responsible for LGA are unclear but it is associated with altered placental development/function. Recent data also shows a link between temporal changes in maternal glucose and LGA; women with GDM that deliver appropriate for gestational age (AGA) infants have a nocturnal reduction in glucose (5.5 mM–5 mM), whereas women that deliver LGA babies have consistently high glucose (7 mM). We hypothesise that glucose fluctuations impact glucose-sensitive transporter expression in the placenta and that this may contribute to LGA. We performed QPCR to determine the levels of GLUT-1, -3, -4, -8, -9, -10 and -12 mRNA in placental tissue. Consistent with previous findings, GLUT-9 and GLUT-12 mRNA expression was significantly increased in GDM ($n=27$) compared to uncomplicated ($n=27$; $P<0.005$) placenta. GLUT-9, which is involved in the transport of both glucose and fructose, was also significantly increased in LGA compared to AGA ($n=13$/group; $P<0.01$) in GDM. To establish if elevated GLUT-9 expression in GDM/LGA may be attributed to changes in maternal glucose, we developed an *ex-vivo* placental explant model to mimic *in-vivo* maternal glucose levels. Tissue from uncomplicated pregnancies ($n=6$) was cultured in consistently high glucose (7 mM; LGA) conditions, or for 18 h in 5.5 mM followed by 6 h in 5 mM glucose (AGA) over 48 h (confirmed by colorimetric glucose assay of media). LDH and hCG analysis (ELISAs) demonstrated that tissue remained viable throughout. GLUT-9 mRNA expression was not altered by glucose. Whilst placental GLUT-9 expression is associated with LGA in pregnancies complicated by GDM, it does not appear to be modulated by acute temporal changes in glucose *ex-vivo*.

DOI: 10.1530/endoabs.65.P362

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Placental expression of progesterone receptor is down regulated in fructose-fed rats

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Maternal diabetes is known to impair placental function; however, its effect on placental expression of progesterone and oestrogen receptors has not been well documented. Fructose feeding has been used to induce insulin resistance in animal models (Suga *et al.,* 2000; Arikawe *et al.,* 2004; Iranloye *et al.,* 2011). The study aimed to assess maternal serum levels of progesterone, oestriol and oestradiol; placental morphology and its expression of progesterone and oestrogens receptors in fructose-induced diabetic rats. Twelve female rats were randomly divided into two groups namely group 1; control rats fed with normal rat chow and group 2; treated rats fed a diet consisting of 25% fructose to induce type 2 diabetes mellitus. Hyperglycaemia and hyperinsulinemia were confirmed after 8 weeks of feeding. Rats in both groups were mated and pregnancy confirmed. Blood samples were obtained and assessed for glucose, insulin, progesterone, oestriol and oestradiol levels. Placental tissues were isolated, weighed and fixed for morphological studies and the expression of oestrogens and progesterone receptors using immunohistochemical technique. Results showed that maternal glucose, insulin and progesterone levels were significantly increased in the diabetic rats with no significant difference in oestriol and oestradiol levels. Placental weight, central thickness and diameter were increased; placental junctional zones were enlarged due to an increase in the number of glycogen and trophoblast giant cells in the diabetic placentae. Progesterone receptor expression was down regulated in the placentae of diabetic rats, while there was no significant difference in oestrogens receptor expression compared to the control placentae. Type 2 diabetes mellitus therefore impairs serum progesterone levels, placental morphology and down regulates placental progesterone receptor expression in pregnant rats.

DOI: 10.1530/endoabs.65.P363

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Retrospective analysis of pulmonary venous drainage in 90 patients with Turner syndrome demonstrates abnormalities are common; Is it time to review the guidelines?

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Turner syndrome is a common chromosomal disorder affecting 1 in 2500 life female births. Turner syndrome is associated with congenital cardiovascular malformations of the aortic arch, systemic and pulmonary venous return with reported incidences ranging from 23 to 45%. These vascular malformations cause significant morbidity and mortality with increased incidence of aortic pathology, right heart strain and pulmonary hypertension as a result. In this investigation we retrospectively reviewed CT-chest and C-MR imaging studies of patients with known Turner syndrome who are under regular follow up in the Oxford Turner Syndrome clinic from January 2010 to August 2018. CT scans and C-MR studies were analyzed by a senior clinician for abnormalities in particular anomalous pulmonary return. Out of 102 Turner patients under regular follow up 90 had undergone either C-MR imaging or a CT-chest since their original diagnosis. 22 out of these 90 patients (24.4%) were found to have abnormal venous connections. Three patients (3.3%) were found to have isolated anomalous left upper pulmonary venous return, seven patients (7.7%) were found to have isolated right upper pulmonary venous return while 3 patients (3.3%) were found to have bilateral anomalous upper pulmonary venous return. 3 patients (3.3%) were found to have anomalous azygous connections, 5 patients (5.5%) had left sided SVCs and 1 patient (1.1%) had an interrupted IVC. Current international guidelines for the management of Turner syndrome patients suggest transthoracic echocardiography and C-MR imaging at the time of diagnosis but specific imaging of the pulmonary vasculature is not recommended. We suggest that initial cardiovascular imaging should include detailed imaging of the pulmonary veins as abnormalities may lead to right heart dilation and subsequent failure. Thus CT angiography or targeted C-MR venogram to assess for PAVD could be performed in addition to assessment of aortic arch anatomy.

DOI: 10.1530/endoabs.65.P364

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Derivatisation of 5α-dihydrotestosterone enhances sensitivity of analysis of human plasma by liquid chromatography tandem mass spectrometry

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Liquid Chromatography tandem mass spectrometry (LC–MS/MS) is gold-standard for androgen analysis in biological fluids, superseding immunoassays in specificity, particularly at low concentrations. While LC–MS/MS is well established for analysis of testosterone (T) and androstenedione (A4), 5α-dihydrotestosterone (DHT) presents greater analytical challenges. DHT circulates at low nanomolar concentrations in men and lower in women, ionising inefficiently. Thus, even using current LC–MS/MS technology, relatively large plasma volumes (>0.5 ml) are required for detection, undesirable clinically and unsuitable for animals. This study investigated stable derivatisation approaches using hydrazine-based reagents to enhance ionisation efficiency and sensitivity of analysis of DHT by LC–MS/MS. Derivatisation of DHT using 2-hydrazino-1-methylpyridine (HMP) and 2-hydrazino-4-(trifluoromethyl)-pyrimidine (HTP) were compared. A LC–MS/MS method was validated a solid-phase extraction (SPE) LC–MS/MS method using an Acquity-QTrap5500, analysing extracts of human plasma (male, pre and post-menopausal women), following SPE using Oasis® HLB (1 cc/10 mg). HMP derivatives were selected for validation being more sensitive than those formed with HTP. HMP derivatives were detected by selected reaction monitoring (DHT-HMP *m/z* 396 → 108; T-HMP *m/z* 394 → 108; A4-HMP *m/z* 392 → 108). Chromatographic separation of androgen derivatives was optimised, carefully separating isobaric interferents. Limits of detection on column were 0.2, 0.4 and 0.2 pg and quantitation were 0.4, 0.8 and 0.5 pg for DHT-HMP, T-HMP and A4-HMP respectively. HMP derivatives of all androgen could be detected in small plasma volumes: male (100 μL) and female (200 μL), and derivatives were stable over 30 days. In conclusion, HMP derivatisation, in conjunction with LC–MS/MS, is suitable for quantitative analysis of DHT and T in small plasma volumes, offering clear advantages in sensitivity over current methodologies. Concomitant analysis of A4-HMP offers similar sensitivity to the underivatized steroid.

DOI: 10.1530/endoabs.65.P365

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The effects of peptide-YY (PYY) on the reproductive axis in humans

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Introduction
Peptide-YY (PYY) is produced by intestinal L-cells following nutrient ingestion. PYY analogues are an emerging class of anti-obesity medication. Peripheral administration of PYY has potent anorectic effects in rodents and humans. Interestingly, rodent studies have demonstrated that PYY has additional effects on reproductive hormone secretion depending on the model studied. In humans, hypogonadism occurs in up to 40% of men with obesity. Therefore, the effects of PYY on the human reproductive axis must be determined to ensure safety of potential PYY-analogues and to understand the interplay between metabolism and reproduction.
Methods
A blinded placebo-controlled crossover study was performed. Eighteen healthy men (age 24.1 ± 0.9 yr; BMI 22.2 ± 0.4 kg/m^2) received an 8-h infusion of 0.4 pmol/kg per min of PYY_{3-36} on one study visit and rate-matched vehicle infusion on a separate study visit, in random order. Blood samples were taken every ten minutes during infusions. Visual analogue scales (VAS: 0–10 cm) were completed by the volunteers pre-, mid- and end-infusion. Blinded deconvolution analysis was used to determine LH pulsatility. Data is presented as mean ± S.E.M.
Results
PYY infusion did not change LH pulsatility (PYY 4.4 ± 0.3 pulses/8 h vs. vehicle 4.4 ± 0.4 pulses/8 h, P>0.99), mean LH (PYY 2.8 ± 0.2 IU/l vs. vehicle 3.0 ± 0.2 IU/l, P = 0.31) and LH AUC (GLP-1 1524 ± 101 IU.min/l vs. vehicle 1484 ± 88 IU.min/l, P = 0.70). Similarly, FSH AUC (PYY 1158 ± 513 IU.min/l vs. vehicle 1199 ± 476 IU.min/l, P = 0.49) and testosterone AUC (PYY 10 485 ± 684 IU.min/l vs. vehicle 11 133 ± 803 IU.min/l, P = 0.24) were unaffected by PYY administration. Mid-infusion nausea VAS scores were higher during PYY infusion compared to during vehicle infusion, although the nausea rating remained clinically low (PYY 2.5 ± 0.5 cm vs. vehicle 1.3 ± 0.3 cm, P = 0.03).
Conclusions
Our results demonstrate that acute administration of a biologically active dose of PYY does not have detrimental effects on the human reproductive axis. This provides important physiological and safety data for the development of PYY-based treatments.

DOI: 10.1530/endoabs.65.P366

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GC-MS-based quantitative steroid signatures reveal different androgenic pathways between fetal and adult mice

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Although the steroidogenesis in testis occur in a paracrine rather than in an endocrine, the comparative metabolic pathways between fetal and adult mice are not fully understood. Here, gas chromatography-mass spectrometry-based assay for profiling of 23 androgens, 7 estrogens, 13 corticoids, and 14 progestagens has been developed and applied to quantify their testis levels from both fetal and adult mice. Testis samples were purified with Oasis HLB solid-phase extraction and separated through a MXT-1 (30 m×0.25 mm I.D., 0.25 μm film thickness, Siltek-treated stainless steel) column prior to GC-triple quadrupole/MS (GC–MS/MS) analysis. The devised assay showed a good linearity (r^2> 0.991) with precisions (%CV) and accuracies (%bias) ranged from 1.1% to 15.4% and from 82% to 117%, respectively. All steroids detected were higher in adult testes, while Δ5-androstenediol (A-diol) was only quantitative in fetal testes, which mean the conversion of DHEA into A-diol may be dominantly occurred during fetal development. In addition, the metabolic ratios of 7α-hydroxylation of androstenedione and testosterone were significantly increased in fetal testes. The metabolic signatures of steroids in testes reflect the comparative steroidogenesis during developmental stages and may useful for monitoring the metabolic response to physiological conditions.

DOI: 10.1530/endoabs.65.P367

P368

A comparison of follow-up rates of women with gestational diabetes before and after the updated National Institute for Health and Care Excellence guidance advocating routine follow-up, and the association with neighbourhood deprivation

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Background

Gestational diabetes mellitus (GDM) occurs in every 23 UK pregnancies. GDM identifies the mother as high-risk for development of type 2 diabetes. The National Institute for Health and Care Excellence (NICE) published updated guidance in February 2015 recommending routine follow-up of women with GDM.

Aims

This cohort study compared follow-up rates of women with GDM before and after the updated guidance. We also investigated for an association between follow-up rates and deprivation.

Methods

Participants were identified from the database of the GDM service of SATH NHS Trust and were organised into two cohorts: 'pre-guidance' (2012–2015) and 'post guidance' (2015–2016). We compared follow-up rates of these two cohorts, using the recommendations of the NICE guidance, the patients' postcodes against the English Indices of Deprivation, to investigate the relative levels of neighbourhood deprivation, of those followed up compared with those not. The Z statistic was used to test for statistical significance.

Results

535 participants were included (pre-guidance $n=306$, post-guidance $n=229$). Baseline average age (pre-guidance 32.2 years, post-guidance 32.5 years), body mass index (30.7 kg/m^2, 30.9 kg/m^2) and fasting glucose (4.9 mmol/l, 4.8 mmol/l) were all comparable between cohorts. The follow-up rate improved from 60.5% in the pre-guidance group to 69.9% in the post-guidance group. The median deprivation rank of those followed up was14 565 compared with 13 393 in those not followed up, which was not significant.

Conclusion

A higher proportion of women with GDM were followed up with screening for type 2 diabetes after the updated NICE guidance in 2015 recommended routine follow-up. Across the study, over a third of women were not followed up with no statistically significant difference in the deprivation levels of those followed up with those not followed up.

DOI: 10.1530/endoabs.65.P368

P369

Investigating placental endocrine dysfunction in a translationally relevant mouse model of fetal growth restriction

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Fetal growth restriction (FGR), which describes the failure of a fetus to achieve its genetic growth potential, not only increases the risk of perinatal mortality and morbidity but also predisposes to metabolic disease in adulthood. In developed countries, FGR is typically attributed to dysfunction of the placenta – a transient organ that mediates nutrient supply, eliminates waste, and protects the fetus from maternal immune response. The placenta also functions as a major endocrine organ, synthesising and secreting an abundance of hormones that act both locally and distally to sustain pregnancy and support fetal growth. The gene *Phlda2* specifically regulates placental endocrine capacity in the mouse, with over-expression of *Phlda2* impairing placental endocrine function whilst loss of function of *Phlda2* enhances this function. In humans, elevated placental expression of *PHLDA2* is frequently observed in FGR, with transgenic mice that over-express *Phlda2* growth restricted relative to control littermates, thus demonstrating a causal role. Surprisingly, both *Phlda2* null and their genetically wild-type 'control' littermates are also growth restricted relative to fetuses from entirely wild-type litters. This may be attributed to the enhanced *in utero* endocrine environment elicited by the *Phlda2* null placentas, with placentas of both genotypes exhibiting excessive glycogen storage that deprives fetuses of nutrients required for growth. We therefore hypothesised that the severity of growth restriction previously attributed to over-expression of *Phlda2* in the mouse is under-estimated. We thus sought to investigate whether exposure to a sub-optimal *in utero* endocrine environment restricts fetal growth and contributes to *Phlda2*-driven FGR. To investigate this, we generated mixed litters comprising fetuses that over-express *Phlda2* and control littermates, with fetal growth and placental function compared with litters comprised entirely of strain-matched wild-type fetuses. Consistent with our hypothesis, we observed adverse effects on fetal growth and placental function, and furthermore identified a complex interaction of environmental factors, including strain-dependent genetic susceptibility and maternal diet.

DOI: 10.1530/endoabs.65.P369

P370

Hyperprolactinaemia resistant to dopamine agonist due to an ectopic source of prolactin arising from a Uterine Tumour Resembling Ovarian Sex Cord Tumours (UTROCST)

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A 46 year old female presented with 12 months history of secondary amenorrhoea. Prolactin was 4746 mIU/l without macroprolactin complexes, LH & FSH were low, oestradiol was undetectable. She had normal visual fields. No other clinical or biochemical features of pituitary dysfunction. She had no regular medication. Pituitary MRI was normal. She was started on cabergoline 250 mcg twice weekly which was subsequently increased to 500 mcg twice weekly. Repeat serum prolactin 5 months and 8 months later showed a progressive rise to 6649 mIU/l and 9653 mIU/l respectively. Compliance with medication was confirmed. Repeat pituitary MRI scan was normal. An alternative source of prolactin was considered. Further clinical assessment revealed a palpable pelvic mass. Pelvic CT showed an 11 cm uterine mass which raised the possibility of an ectopic prolactin source. She underwent surgical resection. Histological examination showed a benign Uterine Tumour Resembling Ovarian Sex Cord Tumours (UTROSCT). Immunohistochemistry was negative for prolactin, however serum prolactin postoperatively reduced to 59 mIU/l and menstrual cycle returned.

Discussion

The notable features of this case were (1) the high prolactin with a normal MRI scan (2) A paradoxical rise in the serum prolactin after initiation of dopamine agonist therapy. Out of 8 previous reports of ectopic extra-cranial prolactin secretion in the published literature, there were three ovarian germ cell tumours (two teratomas, one dermoid) which showed microscopic pituitary elements. UTROSCTs are rare uterine neoplasms with the most recent literature review

citing 77 cases. UTROSCTs have not been associated with hyperprolactinaemia prior to this report. However, two other cases have been reported with uterine tumours (one 'fibroid' and one 'mesenchymal tumour') which share characteristics with this case. Hyperprolactinaemia due to extra-cranial ectopic prolactin production is rare. Where suspected, the majority of ectopic prolactin-secreting tumours have been located in the ovaries and uterus.

DOI: 10.1530/endoabs.65.P370

P371

Polycythaemia in a Klinefelter syndrome population on testosterone

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Background
Klinefelter syndrome (KS), karyotype 47XXY, affects 1 in 650 males. Subjects develop primary gonadal failure requiring life-long testosterone replacement. Many different testosterone formulations are available and long-term monitoring is necessary to avoid secondary polycythaemia.
Objective
To investigate the effect of testosterone formulations used in KS subjects and estimate frequency of association with secondary polycythaemia.
Method
A single institution retrospective review of the hospital database was undertaken to identify KS subjects. Collated data included formulation of testosterone replacement and evidence of secondary polycythaemia – defined as either a haemoglobin > 170 g/l or a haematocrit > 0.54 l/l.
Results
83 subjects with KS were identified. 72 subjects (87%) took some form of testosterone or hCG. Of these 72 subjects, 34 (47%) took testosterone undecanoate (Nebido), 7 (10%) took testosterone esters (Sustanon), 23 (32%) took topical testosterone gel (Testogel or Tostran) and 8 (11%) took Pregnyl/Gonasi. 10 of 72 (14%) subjects had evidence of polycythaemia at some point during follow-up. In 2 subjects, both the haemoglobin and haematocrit were raised; only the haemoglobin was raised in the remaining 8 subjects. 7 subjects took testosterone undecanoate (intervals: 13 weekly(1); 12 weekly(4); 10 weekly(1) and 750 mg 20 weekly(1)) and 3 took daily testosterone gel subjects (Testogel(2) and Tostran(1)) – 20.5% of subjects taking testosterone undecanoate and 13% of subjects taking testosterone gel developed polycythaemia. 2 subjects (one taking Nebido, the other Testogel) required venesection as treatment for polycythaemia, with others only requiring dose alteration.
Conclusion
A significant minority of KS subjected developed polycythaemia whilst on testosterone therapy. Testosterone undecanoate appears to be associated with the highest risk despite published data reporting a relatively low risk with this preparation. In the KS cohort, avoidance of polycythaemia is important given the increasing risk of venous thromboembolic disease with age.

DOI: 10.1530/endoabs.65.P371

P372

Turner syndrome and fertility discussion: food for thought from patients

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Due to decreasing ovarian reserve from young age, counselling is vital as chances to conceive spontaneously decrease rapidly and early consideration of fertility options essential. Maternal/fetal-risks are high and patients/specialists face important considerations.
Aim
Service-evaluation of adequacy/appropriateness/sufficiency of information about fertility provided to TS patients.
Methods
TS women attending two TS-dedicated-centres participating in The-Reproductive-Life-Course-Project were invited to complete an anonymous fertility discussion questionnaire.
Results
105 participants, 33 years, 8 spontaneous, 9 assisted-pregnancy, one adopted. 47/105 provided comments. Timing of fertility discussion was in 45% at 16–25y, considered the optimal-age in 47%, 27% suggested 10–16y, 15% 25–35y. 24% would have preferred another time, 56% later. Importantly, 15/47 felt the discussion should occur earlier, although 4/47 suggested it should be patient originated. Fertility was discussed by one specialist/figure in 51%; mainly by Adult-Endocrinologist (43%). For 79% the suggested approach was by multiple specialists/figures, including mainly Adult-Endocrinologist (36%), along with parents/GP/Pediatric-Endocrinologist; 16% suggested another TSwoman. 2/47 commented discussion should be conducted by informed-specialists. Only 9% felt they received complete information. Oocyte-donation was discussed in 50%, cardiac-risks in 31%, adoption in 27%, fetal-risks in 15%. Insufficient ($<$6.0–10 scale) information was provided in 44%. 17% received written information/website details. 19/47 would have liked more information, 4 specifically about cost/funding of assisted-pregnancy, 4 about pregnancy-related risks. 41% used Turner-Syndrome-Support-Society website, 72% found sufficient (>6) information. 6/47 felt that ongoing/repeated discussion was important, 13% that discussion should be honest/open, 4% emphathic. Discussion should consider sexuality (2/47), psychological-impact of infertility (2/47), cultural-angle (1/47).
Conclusions
This is the first study assessing TS women's perspective, highlighting areas requiring improvement. Our data emphasize the importance of an individualised-approach in terms of timing, of early often-repeated discussions, conducted by TS-dedicated-specialists, involving parents/GP and TSSS for web-literature-information and experience/support from other TSwomen.

DOI: 10.1530/endoabs.65.P372

P373

Should SHBG be measured in every patient before diagnosing hypogonadotrophic hypogonadism?

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Case
A 19-year-old British-Asian man presented with a two-year history of gynaecomastia. He had no other symptoms of hypogonadism. On examination, BMI was 28 kg/m^2 and he had post-pubertal-sized testes (20 ml) with normal secondary sexual characteristics. Hypogonadism was confirmed by two morning fasting total testosterone levels of 4.7 and 5.2 (RR 9.2–31.6 nmol/l). Haemoglobin was normal (152 g/l) and serum oestradiol was $<$100 pmol/l. He had inappropriately normal serum gonadotrophin levels: LH 1.2 (RR 1.2–7.8 iU/l), FSH 2.1 (RR 2.0–5.0 iU/l) consistent with hypogonadotrophic hypogonadism. Other pituitary hormone levels and MRI pituitary were normal. In view of his biochemical hypogonadism, he was started on testosterone replacement therapy. A DEXA scan following six years of testosterone replacement showed Z scores of $-$2.1 in the spine and $-$1.3 in the hips. Seminal fluid analysis was normal on several occasions and he had fathered a child. He was re-evaluated following 7yrs of testosterone therapy. Both pituitary-function tested with a 100 mcg GnRH test, and hypothalamic-function tested with a kisspeptin-54 challenge test, were consistent with responses of healthy men. His sex hormone binding globulin (SHBG) was found to be consistently low at 6 (RR 15–55 nmol/l). His calculated free testosterone level by the Vermeulen equation was found to be borderline at 0.251 (RR >0.225 nmol/l). His father's SHBG was also found to be very low at 4 nmol/l (father's BMI 24 kg/m^2) consistent with a rare inherited SHBG mutation (analysis pending).
Conclusion
The interpretation of serum gonadotrophins relies on the initial determination that testosterone levels are consistent with hypogonadism. Endocrine Society

guidance suggests that SHBG does not need to be measured unless the testosterone level is borderline, or conditions that could affect the SHBG level exist. This case highlights the potential for misclassification of gonadal function if unexpectedly low SHBG levels are not considered when evaluating patients presenting with possible hypogonadism.

DOI: 10.1530/endoabs.65.P373

P374

Diagnostic evaluation of polycystic ovarian syndrome: how the biochemistry stacks up against subsequent ultrasound scan evaluation

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Background
Polycystic ovarian syndrome (PCOS) is a common endocrine disorder in women of reproductive age. PCOS is associated with future type 2 diabetes/cardiovascular disease. Accurate diagnosis is important for early preventative interventions. However, it can take >2 years and contact with 3 or more health professionals before PCOS is diagnosed. We aimed to determine patterns of biochemical investigations performed for PCOS following initial consultation and assess their influence on subsequent radiological investigations.
Methods
Using a hospital radiology database between 2010 and 2015 to identify the study population, data was collected on biochemistry investigations performed within the 2-year period before imaging.
Results
Out of 206 women who underwent pelvic ultrasound scan (USS) and biochemical investigations, a large number of combinations ($n=47$) of biochemical investigations were requested at initial consultation before USS. The number of tests performed prior to USS varied from a single test to the full panel of seven tests. There was an inverse relation between the number of biochemistry tests at initial venepuncture episode and 'time to scan'. Those who had <3 tests had significantly longer time from first request to pelvic USS (median time 70 days) than those with 3–7 tests (median time40 days; $P=0.002$, HR = 1.6; 95% CI 1.2–2.2). FSH and LH were in the top 5 most common biochemical test panel in 53% of study population. Women with LH:FSH ratios >2 or testosterone levels >2.5 nmol/l were more likely to have PCO confirmed on USS ($P<0.02$), compared to women with lower ratios or levels. Serum testosterone levels were higher in PCOS women.
Conclusion
We have not found any identifiable pattern to biochemical investigations requested as part of the initial diagnostic evaluation for PCOS. Standardization of the initial biochemical panel of analytes for PCOS workup has the potential to improve efficiency and diagnostic yield with consequent patient benefit.

DOI: 10.1530/endoabs.65.P374

P375

Audit of premature ovarian insufficiency management at University Hospitals Leicester NHS Trust

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Background
Premature Ovarian Insufficiency (POI) is characterised by oligo-/amenorrhoea with elevated gonadotropins and low oestradiol before the age of 40 years.
Objective
To evaluate management of non-Turner POI patients in line with European Society of Human Reproduction and Embryology (ESHRE) guidance (1)
Methods
Retrospective evaluation of electronic and paper case records.
Results
Over 23-year period (1995 to 2018), $n=53$ were included in audit; 75 cases reviewed, 22 excluded due to incomplete data and erroneous coding. Mean age at diagnosis- 33 years; mean BMI 25.5 (17–39.4 kg/m^2). Mean duration of oligo/-amenorrhoea 13 months. Aetiology of POI: Autoimmune-16, total body irradiation/chemotherapy-4, HIV-3, thalassaemia-3, oophorectomy-2, Idiopathic POI-25. Ovarian antibodies were negative ($n=19$ assessed); adrenal autoantibodies negative ($n=3$ assessed); 35/51 (66%) not assessed for cortisol reserve at diagnosis; 7 patients had osteopenia/osteoporosis.

ESHRE guidance	Compliance
Biochemical diagnosis 2 FSH levels of >25 iu/l 4 weeks apart	53/53 (100%)
Genetic testing/Karyotyping	11/25 (44%)
Autoimmune endocrine screening	26/53 (49%)
Cardiovascular risk screening	None recorded apart from hypertension- therefore 0%
Bone health assessment	47/53 (88%)
Fertility services referral is appropriate	Joint Gynae-Endo clinic (100%)
Hormone Replacement therapy (HRT)	53/53 (100%)
Patient education leaflets, website etc.	0% recorded in notes

Discussion
There was considerable delay in patients seeking medical attention from the onset of symptoms: 13 months compared to ESHRE guidance of 4 months. We were compliant in measures such as HRT, bone health assessment but suboptimal in genetic testing, autoimmune screening, cardiovascular (CV) risk monitoring and patient information dissemination; following interventions are proposed:
1. Annual metabolic profile & advice regarding CV risk reduction.
2. Clinical assessment of autoimmune conditions.
3. Referral to clinical genetics for evaluation.
4. POI patient information dissemination.
5. Explore ways of improving public health awareness of POI with help of primary care colleagues.

Reference
1. ESHRE POI guidelines, December 2015.

DOI: 10.1530/endoabs.65.P375

P376

Too much of a good thing – two cases of severe dilutional peripartum hyponatraemia with lessons to learn

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Peripartum hyponatraemia is an under-recognised complication of labour and poses a risk to both mother and baby. It is typically caused by water intoxication for physiological reasons and population health trends around water intake. We have recent experience of managing 2 patients with severe symptomatic hyponatraemia. Both patients had increased their oral intake of fluid during labour as well as receiving intravenous fluids. Dilutional hyponatraemia was found to be the underlying cause in both cases. Initial treatment with hypertonic saline and subsequent fluid restriction rapidly corrected the hyponatraemia though both patients had a prolonged length of stay, required intensive care admission and neonatal assessment and treatment. We have since surveyed our midwifery and medical staff showing gaps in knowledge of this condition – 60% not aware of the risk of hyponatraemia in labour, 45% not aware of associated complications and 40% not knowing the most appropriate management strategy. Through a multidisciplinary approach involving endocrinology, obstetric, anaesthetic and midwifery teams, we have introduced a new approach of monitoring fluid balance during labour and checking sodium if fluid intake exceeded >2.5 l or fluid balance is >1.5 l positive. We have introduced a local labour ward guideline for the management of severe symptomatic hyponatraemia in labour and created an education package for all midwifery staff.

DOI: 10.1530/endoabs.65.P376

P377

A systematic review of randomized controlled trials investigating the efficacy and safety of testosterone therapy for female sexual dysfunction in postmenopausal women

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Introduction
Over half of postmenopausal women suffer symptoms which can sometimes be non-responsive to hormone replacement therapy (HRT). Testosterone is implicated in regulating urogenital and sexual function in women. However, using testosterone therapy in postmenopausal women remains highly controversial, principally due to the lack of syndromic relationship between serum testosterone levels and onset of sexual dysfunction during menopause. Clinical practice is therefore highly variable worldwide.
Aim
Objectively summarise published literature investigating the effectiveness and safety of testosterone replacement for sexual dysfunction in postmenopausal women.
Methods
Searches of CENTRAL, EMBASE, MEDLINE and PubMed were conducted. Search was in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology to find all randomized placebo controlled (RCT) studies of testosterone therapy in women.
Results
A total of 26 randomized placebo controlled (RCT) studies suggest that testosterone therapy significantly improves symptoms of sexual dysfunction. However, eight RCTs showed no significant difference for menopausal symptoms between testosterone therapy and placebo groups. Most studies conclude that testosterone therapy has no significant beneficial effect on reducing hot flash frequency and severity. Finally, exogenous testosterone increases haematocrit and there is hardly any long-term safety data on thromboembolic disease in postmenopausal women using testosterone.
Conclusion
Majority of RCTs suggest that testosterone therapy significantly improves sexual function in postmenopausal women with sexual dysfunction or hypoactive sexual desire disorder. Testosterone therapy in postmenopausal women is well-tolerated in the short-term however, there is a paucity of long-term safety data. We recommend that testosterone therapy could be considered for the minority of postmenopausal women for whom other management strategies have failed.

DOI: 10.1530/endoabs.65.P377

P378

Role of risk factors for gestational diabetes mellitus in determining newborn outcomes in a Nigerian teaching hospital

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Introduction
Gestational diabetes mellitus (GDM) is a common metabolic disorder. The risk factors for GDM are often employed in selective screening. The impact of risk factors for GDM on newborn is yet to be fully evaluated.
Objective
To determine the impact of maternal clinical risk factors for gestational diabetes mellitus on the anthropometric and clinical outcomes of the newborns.
Method
The study was a prospective open cohort study carried out from March 1st to November 2017 at the Lagos University Teaching Hospital (LUTH), Lagos; Nigeria. Ethical approval obtained from LUTH ethics committee. All the pregnant women were categorized into either risk group or control group based on the presence or absence of clinical risk factors for GDM. They all had 75 g OGTT done at 24 to 28 weeks gestation. The women and babies were followed up till delivery. The pregnant women were categorized into those with single, two and more than two clinical risk factors for GDM. Anthropometric measurements of the newborn that were done were birth weight, chest, abdominal and head circumference. The *P* value of less than or equal to 0.05 was considered significant.
Results
Ninety pregnant women were recruited in the course of the study. About 24% of the pregnant women had GDM based on IADPSG criteria. There were eight deliveries of macrosomic babies. More than 60% of the deliveries of macrosomic babies occurred in women with more than three risk factors for GDM. There were higher occurrences of birth trauma, neonatal ward admissions in newborns of women with multiple risk factors for GDM.
Conclusion
Assessment risk model using more than two maternal clinical risk factors for GDM could be employed to evaluate the risk of adverse fetal outcomes in resource poor settings
Conflict of interest
we declare no conflict of interest
Keywords
GDM, Gestational Diabetes Mellitus
DOI: 10.1530/endoabs.65.P378

P379

Infertility in a man with Sertoli cell-only syndrome and 47,XYY karyotype

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A 32-year-old man presented with a four year history of reduced libido, erectile dysfunction and inability to conceive with his partner. He went through puberty normally and had a normal sense of smell. Clinical examination revealed that he was 205 cm tall and normally virilised. Testicular volume was reduced, but the phallus was normal. Clinically, he appeared euthyroid and there were no features of hypercortisolism or growth hormone excess. Biochemical picture: prolactin 375 (nr $<$ 350 mU/l), testosterone 15.9 (10–28 nmol/l), follicle stimulating hormone 39.0 ($<$12.0 U/l) and luteinising hormone 23.6 ($<$9.0 U/l). Pituitary MRI revealed an enlarged pituitary gland (14 $\times$ 11 $\times$ 10 mm) extending into the suprasellar cistern with minimal optic chiasmal compression. Perimetry revealed a normal left visual field and 2 spots missing in the periphery of the right visual field. Karyotyping revealed 47,XYY. Ultrasound testes showed a 1.5 cm focal rounded area of ill-defined abnormality for which he underwent left testicular orchidectomy and right testicular biopsy. Histology revealed Sertoli cell-only syndrome. The pituitary surgical opinion was to observe with annual MRI pituitary scans and visual field examinations. The patient was treated with Cabergoline and Tadalafil. He was referred to the fertility clinic where his partner underwent donor insemination and delivered a healthy baby. The enlarged pituitary in our patient seems to be on account of pituitary gland hyperplasia with macroadenoma being a differential. Sertoli cell-only syndrome is a rare cause of infertility and should be considered in men aged 20–40 years with a normal karyotype. However, in our patient, the karyotype was abnormal (47,XYY), which is another cause of infertility. Our rare and complex case highlights the importance of considering more than one cause of infertility and the need to involve a multidisciplinary team (endocrinologist, pituitary surgeon, andrologist, histopathologist, geneticist, ophthalmologist) to unmask the diagnostic web.

DOI: 10.1530/endoabs.65.P379

P380

Seeing is believing – is that always true?

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Introduction
Hirsutism affects 10% of the female population caused by hyperandrogenism of benign aetiologies or androgen-secreting tumours. Tumorous causes of

hyperandrogenism include androgen producing ovarian or adrenal tumours. Leydig cell tumours are rare ovarian testosterone producing tumours that comprise 0.1% of total ovarian tumours. It is rare in postmenopausal women and present with features of hyperandrogenaemia or hyperestrogenemia.
Case
We present the case of a 58-year-old post-menopausal woman with a 6-month history of virilisation characterized by rapidly progressive hirsutism, alopecia, and deepening of her voice. The diagnostic evaluation showed elevated testosterone (11.6 nmol/l) with normal dehydroepiandrosterone sulphate (DHEAS). CT abdomen, MR pelvis and a transvaginal ultrasound revealed normal ovarian morphology and left adrenal nodule (8 mm). This created the diagnostic dilemma with suspicion of adrenal tumour producing hyperandrogenaemia, as isolated testosterone producing adrenal tumours has been described in the literature. However, the postmenopausal status of our patient, normal DHEAS levels, the decision was made to do bilateral oophorectomy in the first step that showed well defined un-encapsulated ovarian Leydig cell tumour. Repeat testosterone 2 weeks post op showed normal testosterone levels (0.3 nmol/l) with significant improvement of wellbeing and the pitch of her voice, confirmed the diagnosis of ovarian Leydig cell tumour as the cause of her virilism with co-existing adrenal incidentaloma.
Conclusion
In the case of equivocal radiological investigations and a biochemical picture of ovarian hyperandrogenaemia, it is reasonable to proceed with oophorectomy for post-menopausal women or women not desiring future fertility. For those wanting to preserve fertility, precise aetiology needs to be worked out by selective venous sampling, measuring other hormonal hypersecretion and measuring androgen suppression by dexamethasone.

DOI: 10.1530/endoabs.65.P380

P381

Effect of endocrine disrupting chemicals on male reproductive health

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Introduction
Endocrine disrupting chemicals (EDC) are exogenous substances altering function(s) of the endocrine system. EDCs have been implicated in the decline in male reproductive health. We aimed to systematically review the pathophysiological effects of EDCs on male reproductive health.
Methods
Searches of EMBASE, MEDLINE and PubMed were conducted using the following terms: 'endocrine disrupt*' OR 'endocrine disruptors' OR 'endocrine disruptor chemicals' AND 'men' ('male' in EMBASE) AND 'sperm*' OR 'spermatozoa'. Thirty human studies fulfilled the inclusion criteria.
Results
Bisphenol A (BPA) found in plastics, was negatively associated with semen motility, morphology and positively associated with sperm DNA fragmentation. Men with higher urinary insecticide levels were observed to have increasing incidence rate of sperm sex chromosome disomy. Higher median levels of arsenic metabolites and phthalate metabolites were associated with below WHO reference sperm concentration and sperm motility. Exposure to p,p-DDE was related to an increased risk of cryptorchidism, hypospadias, low sperm count and testicular cancer.
Discussion
Evidence suggests that a growing number of EDCs adversely affect sperm quality and reproductive health in men. The full, transgenerational effects of these chemicals need to be investigated to determine the potential cumulative adverse effects of EDCs on male reproductive health in successive generations. Some countries have already established regulations to remove EDCs from everyday products. These results warrant the use of alternatives to EDCs.

DOI: 10.1530/endoabs.65.P381

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An evaluation of the current clinical care pathway of patients referred to a large UK Tertiary Centre with suspected PCOS

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Background
PCOS is a common female endocrine disorder, exacerbated by obesity. International guidelines therefore suggest weight loss as first line management. This service evaluation assessed the care pathway of patients referred to Queen Elizabeth Hospital Birmingham (QEHB) with suspected PCOS. We aimed to assess the referral wait time, reason for referral, treatment offered, and weight management in clinic.
Methods
We undertook a cross-sectional study of retrospective data. We assessed a dataset of 378 clinically phenotyped women with suspected androgen excess that attended QEHB over a 5-year period. We excluded: patients without a diagnosis of PCOS ($n=150$), those added to the dataset before 2016 ($n=168$), and those with unavailable hospital records ($n=11$). Hence, 49 patients were included. The following data were obtained from the electronic records, coded and analysed using Microsoft Excel: age, dates of referral and clinic appointments, reason for referral, type and time of treatment initiated, and BMI at first and last clinic appointment.
Results
Most women were seen within 18 weeks, but 11% did not meet the 18-week target. The most common presenting complaints were androgen excess (80%, $n=39$), and oligomenorrhoea/amenorrhea (78%, $n=38$). For management, 37/49 outpatients were recommended oral contraceptive pills (51%), metformin (45%) or other pharmacological treatment. Of the patients with BMI data available (34/49), 56% ($n=19$) gained weight after their first appointment whilst 34% ($n=12$) lost weight. The patient with the greatest increase in BMI (9.7 kg/m^2) was seen over 9 years. Moreover, for 19% (5/35) of overweight patients, weight management advice was not given at the first clinic, and for those who received this, only 40% had a reduction in BMI.
Conclusions
There is sub-optimal weight management for those patients despite weight counselling in clinic. This supports the need for a comprehensive PCOS service for patients, including contact with a dietician and regular weight follow-up.

DOI: 10.1530/endoabs.65.P382

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A retrospective analysis of side effects of testosterone replacement therapy (TRT)

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Aim
To assess side effects of testosterone (TRT).
Introduction
TRT in men with hypogonadism helps improve libido, erectile dysfunction, energy levels and bone density. However the risks/benefits of TRT in terms of ischemic heart disease (IHD), stroke and venous thromboembolism (VTE) is controversial no definitive answers from current evidence. We evaluated the side effects of TRT in patients attending endocrinology outpatient clinic between 2009 to 2019.
Methods
A retrospective analysis for 106 patients with data collected from electronic clinic letters, blood results and radiology reporting including age, reason for TRT, duration of treatment, past medical history, side effects, time interval between starting TRT and onset of side effects with emphasis on cardio/cerebrovascular outcomes was conducted.
Results
Mean age was 57 years (18–89) and mean duration of TRT was 6 years (1–34). Of 106 patients, 27 had primary, 44 secondary and 38 mixed hypogonadism. Before initiation of TRT, 34 (32.1%) patients had pre-existing diabetes, 43 (40.6%) hypertension, 9 (8.4%) IHD, 6 (5.6%) hyperlipidemia and 2 (1.9%) VTE. During

the study period, 8 (7.5%) patients were diagnosed with IHD, 3 (2.8%) with diabetes and 2(1.9%) each with hypertension, VTE and prostate cancer. Raised haematocrit was observed in 10(9.4%). Average time lag for diagnosis of a new medical condition or a side effect was 3.7 years (range 1–13) after starting TRT while cardiac symptoms had an average time lag of 1.9 years(range 0.5–5). Of 6 patients with pre-existing IHD 4 (50%) showed increased cardiac symptoms.
Conclusion
In our study, very small percentage of patients developed IHD and VTE and none developed stroke after starting TRT. While cardiac symptoms worsened in 50% men with preexisting cardiac disease, no major cardiovascular events occurred. So we feel it is safe to prescribe TRT irrespective of age or pre-existing IHD with cautious monitoring.

DOI: 10.1530/endoabs.65.P383

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Its not just the baby that grows in pregnancy

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Pituitary apoplexy is a rare but life threatening condition if not diagnosed and treated promptly. Common causes include hypertension, head trauma, major surgery, dynamic pituitary tests, anticoagulant use and pregnancy. In pregnancy, hyperplasia and hypertrophy of the lactotroph cells increase pituitary volume by 45% returning to original size at 6 months *post-partum*. Pituitary apoplexy is uncommon in pregnancy and an underlying adenoma is usually the cause. Very few case reports mention pituitary apoplexy due to physiological enlargement in pregnancy. We describe a similar case here. A 30-year-old primi-gravida presented to the Ambulatory Clinic in her 26th week of gestation with a significant dull central headache for the previous three days. There was no past medical history of note and she was only taking folic acid. There was no family history of hypertension, polycystic kidney disease or Berry aneurysms. There were no signs of meningeal irritation with normal visual fields to confrontation. Her blood pressure was 135/75 mmHg. An MRI/MRV brain revealed an 8 mm(8 mm intra-glandular pituitary bleed in T1-weighted images with no compression of the optic apparatus. Further work-up revealed plasma Cortisol 420 nmol/l, TSH 1.88 mIU/l, fT4 11.2 pmol/l and Prolactin 424 mIU/l. She was closely followed up in endocrine clinic and delivered a healthy baby at completion of gestation. A repeat MRI pituitary *post-partum* showed a small reduction (8 mm$\times$7 mm) in the bleed and her biochemistry and endocrine profile remained unremarkable. This case highlights a rare condition during pregnancy which can be detrimental with poor maternal and foetal outcomes. Headache (94%), visual field defects (47%) and nausea and/or vomiting (41%) are the most common clinical features of pituitary apoplexy. This should remain in the differential diagnosis for a physician when a pregnant lady presents with above and should lead to prompt investigations and treatment. A multidisciplinary approach provides the best care in such patients.

DOI: 10.1530/endoabs.65.P384

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Osteoporosis with hypergonadism-2nd time lucky

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A 20 year old man otherwise fit and well, presented with a seizure, fall and fractured neck of femur. DEXA scan revealed osteoporosis; baseline blood tests were apparently normal in the endocrinology clinic with a Testosterone level of 24.3 nmol/l (Range 9.9–27.8) and normal bone and thyroid profile. He was then lost to follow-up. 4 years on, he was re-referred to the endocrinology clinic with a surprisingly elevated testosterone level of 34.6 nmol/l in combination with osteoporosis, Further investigations showed FSH 64.2 IU/l (Range 1.0–12.0) and LH 22.6 IU/l (Range 0.6–12.1) to be raised. He was noted to be of medium build with a male pattern hair distribution and full beard, normal penile length with testes size of borderline volume of 15 ml. He was not in a relationship but claimed to have had normal sexual development on par with his peers, SHBG came back as very high at 142 nmol/l (Range 14–71); bioavailable testosterone was calculated to be low at 5.32 nmol/l. Genetic testing revealed Klinefelter's Syndrome with mosaicism of 46XY/ 47XXY. Topical testosterone resulted in significant improvement in general wellbeing. Mosaicism is seen in 10% of Klinefelter's cases and is less often diagnosed due to the milder phenotype as seen in our patient; a high index of suspicion is needed for diagnosis. SHBG is often elevated and cannot be explained simply by the elevated oestradiol in Klinefelter's. Diagnosis was complicated in this case by the patient being on first generation of antiepileptics also contributing to the SHBG elevation. Although the most common cause of primary hypogonadism with an incidence of 1 in 750, 75% of cases of Klinefelter's are never diagnosed and many are diagnosed later in life. Delay in diagnosis often leads to irreversible physical, mental and social health consequences.

DOI: 10.1530/endoabs.65.P385

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Female hyperandrogenemia, Think beyond the common: A rare case of ovarian Sertoli-Leydig cell tumour

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We describe a 39-year-old lady who was managed as polycystic ovarian syndrome for nearly six years with an initial testosterone level of 5 nmol/l (0–1.8 nmol/l). She underwent laparoscopic ovarian drilling surgery followed by two unsuccessful IVF cycles for primary infertility. Deranged liver function and subsequent diagnosis of non-alcoholic fatty liver disease halted third trial of IVF. At that time, pelvic ultrasound demonstrated five follicles in both ovaries. In addition, a 2.3 cm$\times$1.9 cm well vascularised echogenic mass in the right ovary was detected. CA 125 was within the normal range. GP referred to Endocrinology clinic for excessive hair growth, hyperandrogenemia and menstrual irregularities. Upon review, whole body hirsutism, masculinisation and breasts atrophy were the predominant manifestation. The patient faced relationship crisis as she was described to be converting to male phenotype by her relatives. Abdominal examination revealed a palpable right-sided mass. Hormonal assessment showed high testosterone 21.2 nmol/l (0–1.8 nmol/l), 17-hydroxyprogesterone 29.9 nmol/l (0–5 nmol/l), Androstenedione 1.8 nmol/l (1.0–12.9 nmol/l). Urinary steroid profile and LDDST excluded adrenal cause of high androgen; therefore imaging studies were arranged for further evaluation. MRI pelvis and transvaginal US supported clinical suspicion of Sertoli–Leydig cell tumour. Consequently, laparoscopic right salpingoopherectomy was performed with histological confirmation of the tumour of low Ki 67$<$ 1%. Post surgery, hirsutism improved, menstrual cycles recommenced regularly with complete normalisation of testosterone 0.7 nmol/l.
Conclusion
This lady was treated for PCOS for years prior to endocrinology referral. Initially, She with severe physical and psychological consequences. Other less common causes of very high androgens should be sought in patients with non-classial presentation. Sertoli–Leydig cell tumour is a rare malignancy accounting for less than 0.5% of ovarian neoplasms. In one-third of the cases, there are hypervirilisation symptoms.

DOI: 10.1530/endoabs.65.P386

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Analysis of efficacy of different formulations of testosterone replacement therapy (TRT)

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Aim
To compare efficacy of different formulations of TRT in treatment of hypogonadism
Background
Different formulations of testosterone are available for treatment of hypogonadism in men. TRT improves libido, sexual function, bone density and general well-being. We analysed data of 106 patients on TRT to compare efficacy of topical and injectable formulations.
Methods
It's a retrospective data analysis of 106 patient receiving TRT between 2009 and 2019. Data was collected from electronic outpatient clinic letters and blood results. It included type of TRT, patient satisfaction in terms of libido, erectile function and general well-being, testosterone levels achieved, patients in whom preparation was changed due to any reason, and in whom PDE5 inhibitors (PDE5I) were added to therapy.Results with different formulations were compared.
Results
Out of 106 patients, 38 received testogel, 35 tostran, 4 testim gel, 40 nebido and 10 sustanon injections. All patients on testim (100%), 9 on sustanon (90%), 28 on tostran (80%), 29 on testogel (76%) and 27 on nebido (68%) reported good effects and satisfaction with therapy. Analysis of testosterone levels showed a mean value (in nmol/l) of 14.6 with testogel, 11.5 with tostran and 9.3, 18.3 and 8.5 with testim, sustanon and nebido respectively. 21 patients were switched from one preparation to other. Out of 21, 6 patients needed a change due to side effects, 4 had poor response, 3 patients each due to low testosterone levels and non-availability of preparation and no data was available for 5 patients. In 22 patients PDE5I were added to TRT,10 out of these were on nebido followed by testogel (7) and tostran (5).
Conclusion
Majority of our patients achieved symptomatic benefits, regardless of type of the preparation they were using, with most successful being testim gel (but only 4 were on testim). Good serum levels were achieved along with 90% satisfaction with sustanon.

DOI: 10.1530/endoabs.65.P387

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When dehydration cured Conn's !

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62 year-old lady with a long history of hypokalaemia, hypertension and a random aldosterone of 786 pmol/l with suppressed renin of <8.0 mU/l at a time when she was taking Nebivolol, perindopril and Felodipine. Her Hypokalaemia improved after addition of Spironolactone and remained above 3.5 mmol/l. Biochemical work up confirmed a diagnosis of Conn's syndrome and her BP control improved after addition of Aldosterone antagonist as above. Adrenal MRI revealed a 13 mm adrenal adenoma on left side. Patient refused surgery and a conservative approach was pursued with reasonable control of BP on 4 agents including Spironolactone. A few months later, she sustained an acute kidney injury secondary to dehydration. Following her recovery from this, over successive weeks antihypertensives were stopped due to hypotension. Eventually Spironolactone was also stopped due to persistent hyperkalemia. Repeat Biochemical testing showed serum aldosterone was <30 pmol/l and normal Renin. MRI Adrenal was repeated that showed a significant reduction in the size of the left adrenal adenoma that measured 7.5 mm$\times$8 mm having previously been 12 mm$\times$15 mm with a radiological evidence of fat necrosis probably due to auto infarction of her adrenal adenoma. This possibly occurred during the period of acute kidney injury, hypotension and dehydration. We present a fascinating case of Conn syndrome in which symptoms resolved following infarction of adrenal nodule due to AKI/dehydration/hypotension.

DOI: 10.1530/endoabs.65.P388

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Late presentation of 46 XX male – a case report

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Introduction
Causes of Primary Congenital Hypogonadism in Males are Leydig cell Agenesis, Cryptorchidism, Chromosome abnormalities (e.g. Klinefelter syndrome, SRY positive 46 XX etc), Enzyme defects include 5α-reductase deficiency. Acquired Primary Hypogonadism includes Testicular torsion, Orchidectomy, Chemotherapy/Radiation toxicity, Orchitis, CKD, Cirrhosis, Sickle cell disease, etc. SRY (SEX determining region Y) is regulatory gene located on Y chromosome and is responsible for bipotential gonad to differentiate into a testis. 46 XX male is rare (1 in 20 000 new-born males) and SRY positivity is responsible for 90% of these subjects. External genitalia of 46, XX SRY-positive males appears normal at birth, and diagnosed later with delayed puberty, small external genitalia and infertility [1].
Case report
62 year old gentleman referred for 'Mood swings' and low testosterone. Facial hair growth, Erections and libido normal. He claimed to have a biological daughter of 25 years age. No history of trauma or infection to genitalia. Examination showed Male external genitalia of Tanner Stage 2. Hormone profile showed undetectable Testosterone <0.07, Raised FSH of 45 and LH of 19.6, 0900 h Cortisol 324, prolactin 228, TFTs normal. Vitamin D low at 22.7. DEXA scan showed L/S T score of -2.6 and left hip of -1.3. Ultrasound of scrotum showed bilateral small testes, with high riding Right testis. Karyotyping showed 46 XX male with SRY mutation positive. Vitamin D replacement given .Started on Testogel, but symptoms didn't resolve, so changed to Nebido. Patient was counselled about Infertility. Referred to Geneticist.
Conclusions and discussions
Literature review shows cases of 46 XX Males associated with Scleroderma [2], Breast cancer [3], Achondroplasia [4] and Speech disorders [5]. Most of cases are diagnosed between the 2nd decade and 4th decade due to Infertility. However, our case is a late presentation with Mood swings, Osteoporosis and Infertility.

DOI: 10.1530/endoabs.65.P389

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A rare case of hyperprolactinaemia

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44 years old lady was referred to Endocrinology Clinic with history of secondary amenorrhea and hyperprolactinaemia (7800), that responded to Cabergolin treatment, which was discontinued after 2 months due to side effects (headaches). There was no galactorrhea or visual field defects. MRI Pituitary initially reported as Empty Sella. Her prolactin levels rose further along with headach after she discontinued Cabergoline (and refused alternatives). She eventually agreed for night time dose of bromocriptine. She initially tolerated low dose of Bromocriptine with biochemical response and monthly menstrual periods returned. After a few months, she discontinued Bromocriptine due to insomnia and lethargy. Cabergoline was restarted but she stopped it when she became pregnant. She had an early miscarriage and was subsequently started on Quinagolide. Serum Prolactin kept fluctuating and was attributed to variable compliance. Repeat MRI pituitary was requested when her Prolactin rose upto 9600 which revealed no evidence of micro or macro adenoma in pituitary fossa which was described as mainly fluid filled consistent with Arachnoid cyst. Short Synacthen Test was normal. We present a rare case of hyperprolactinaemia in which imaging was consistently negative for Pituitary adenoma but evidence of Arachnoid cyst and Empty sella.

DOI: 10.1530/endoabs.65.P390

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Non-classical congenital adrenal hyperplasia: a case report in a developing country

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Introduction
Congenital adrenal hyperplasia (CAH) is an endocrine disorder due to deficient adrenal corticosteroid synthesis inherited in an autosomal recessive manner. It is characterized by reduced negative feedback inhibition of cortisol with or without alteration in adrenal mineralocorticoid and androgen secretion. Ninety percent of cases of CAH is due to 21-hydroxylase deficiency. Classical CAH presents in new-born or in early childhood with ambiguous genitalia and/or salt wasting crisis with hypotension. In a less severe form of the disease, patient presents in teenage years to early adulthood with virilising symptoms.
Case report
A 19 year old lady referred from gynaecology clinic on account of absence of menstruation. She also noticed enlargement of the clitoris of about 8 years earlier. No history of baldness, male pattern of hair distribution or deepening of the voice. There is associated excessive acne and thickening of the skin of the face. No nausea, vomiting or dizziness. No known family history of a similar problem. Examination revealed a young woman, conscious, pubic hair and breasts are Tanner stage 5. Weight was 62 kg, height 1.5 m with a BMI of 27.6 kg/m^2. Blood pressure was 100/70 mmHg. Genitourinary examination showed enlarged clitoris. Results of investigations revealed LH 3.78 mIU/ml (0–12), FSH 1.72 mIU/ml (1–9), progesterone 40.4 ng/ml (0.9–35), Prolactin 8.03 ng/ml (1–15), Testosterone 6.25 nmol/l (Female 0.7–2.8), oestradiol 85 pg/ml, Serum DHEA 155 ug/dl (145–395). Serum 17-OH progesterone 79.46 nmol/l (0.13–1.41). Buccal smear showed cellular smears with sheets of superficial and intermediate squamous epithelial cells with abundant cytoplasm and small nuclei. The nuclei contain barr bodies at their periphery in more than 30% of cases. Pelvic ultrasound scan shows rudimentary uterus with regular outline and preserved endometrial echotexture. Genetic testing and 21α hydroxylase enzyme were not done due to financial constraints.
Conclusion
Non-classical congenital adrenal hyperplasia may be investigated for in patients with primary amenorrhoea.

DOI: 10.1530/endoabs.65.P391

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Investigations on reproductive hormones associated – effects of contraception in women

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Contraception is the use of artificial techniques in preventing pregnancy as a consequence of sexual intercourse by many women around the world. This study was carried out to investigate the biochemical effects of contraception on reproductive hormones in women using contraceptives. One hundred and eighty (180) women using different methods of contraception, were recruited for this study from Ekiti State University teaching hospital, Ado-Ekiti, Ekiti State, Nigeria, having obtained ethical clearance. The subjects were divided into six groups based on the contraceptive method used. Group 1 served as control (women using natural planning method), Group 2 (women using oral pills), Group 3 (women using intra uterine device, IUD), Group 4 (women using implant), Group 5 (women using injection) and Group 6 (women using condoms). Parameters including Body mass index (BMI) and some major reproductive hormones were estimated in the plasma of all the groups, using Enzyme linked immunosorbent Assay (ELISA). The results showed significant increase in the BMI of women using pills, IUD, Implant and Injection ($P<0.05$). Significant increases were observed in the concentration of Progesterone and Oestrogen in women on injection, IUD and Oral Pill users ($P<0.05$). However, Significant decrease were observed in the levels of Prolactin, Follicle stimulated hormone and Testosterone in same women using injection, IUD and Oral Pills. Hence, it can be said that reproductive hormones are implicated with the use of contraception, especially in the methods outside the natural and the use of condoms.

DOI: 10.1530/endoabs.65.P392

Thyroid

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Investigating the mechanism behind sodium-iodide symporter trafficking by the small GTPase ARF4

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Dysfunctional regulation of sodium-iodide symporter (NIS) trafficking can result in ineffective radioiodide uptake in patients with differentiated thyroid cancer. Understanding the trafficking pathways of this key protein can be used to optimise radioiodide therapy. Recently, we identified via HiLo microscopy that the protein ADP-ribosylation Factor 4 (ARF4) helps shuttle NIS to the plasma membrane. To understand how ARF4 interacts with NIS mechanistically, we utilised advanced imaging techniques, primarily using Zeiss 780 confocal microscopy to generate 3D images of NIS-GFP and ARF4-mCherry expressing cells. This allowed us to investigate the location of interaction and how this may be manipulated to maximise trafficking towards the plasma membrane. Targeted mutagenesis of the small GTPase ARF4 indicated that the interaction between NIS and ARF4 occurs independently of guanine-nucleotide binding status. Two compounds reported to induce ARF4 expression, phorbol 12-myristate 13-acetate (PMA) and γ-tocotrienol, were tested for their capacity to upregulate ARF4 expression, but neither compound significantly altered ARF4 function in thyroid TPC1 and breast MDA-MB-231 cell lines. Analysis of data from The Cancer Genome Atlas revealed that lower ARF4 expression significantly correlates with positive BRAF mutation status in papillary thyroid tumours. Tetracycline inducible cell lines expressing myc-BRAF were therefore used to investigate whether BRAF is able to regulate ARF4 function. However, ARF4 expression was not affected following induction of BRAF protein levels over time, nor by the mutational status of BRAF, suggesting the MAPK pathway is not a direct regulator of ARF4 expression. Further elaboration of the post-translational pathways involved in shuttling NIS to the plasma membrane is now required to discern how these may be targeted therapeutically to optimise iodide uptake for patients with therapeutically insufficient levels of radioiodine uptake.

DOI: 10.1530/endoabs.65.P393

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Correlation of hormonal analysis in pregnant women with subclinical hypothyroidism and comparison of pregnancy outcome in hypothyroid pregnant women with euthyroid pregnancies

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Background
Pregnancy is a state where changes in maternal physiology influence thyroid status. In addition, thyroid disease in mother can have substantial adverse outcome on the pregnancy and fetus. The objective of this study was to establish correlation of maternal TSH with PAPP-A, Beta HCG, Inhibin, uE3, AFP and HCG and compare pregnancy outcomes in subclinical hypothyroid pregnant women with euthyroid women.
Methodology
110 out of 150 singleton pregnant women were recruited randomly and analysed from high risk antenatal clinic at tertiary care institute in State of Uttar Pradesh, North India for a period from June 2015 to June 2019. Multiple and IVF conceived pregnancies and those with gross congenital malformation were omitted. They were grouped in Group A ($n=60$) with Normal TSH values at time of booking and Group B ($n=50$) with values more than 2.5 miu/l. The medical records were retrieved from the centralized database. Biochemical screening, antenatal complication and pregnancy outcome were noted and compared between the two groups.

Statistical analysis
comparison was done with the statistical software SPSS version 20. T test was performed for independent variable testing and chi square was used for logistic variables. Confidence interval was 95% and P value was <0.05 considered significant.
Results
Significant correlation was found TSH values and Birth weight. 31.42% of neonates were low birth-weight in study group vs. 13.34% in control group. Alfa-fetoprotein, Human chorionic gonadotrophin and Inhibin A were positively correlated and uE3, PAPP-A and Beta subunit of human chorionic gonadotrophin were negatively correlated with levels of TSH, though this was not significant.
Conclusion
Subclinical Hypothyroidism is endemic in northern India. Early diagnosis and prompt treatment can improve pregnancy outcomes and prevent foetal complications. Efforts of triaging the diagnostic modalities with other biochemical markers can offer better risk analysis and help in management strategies.

DOI: 10.1530/endoabs.65.P394

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Thyroid dysfunction is common in hospitalised patients with pre-existing levothyroxine treated hypothyroidism

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Background
Levothyroxine replacement for hypothyroidism is safe and effective but may be associated with reduced quality of life and serious adverse effects if administered inappropriately. We set out to investigate if thyroid hormone profiles in hospitalised patients on levothyroxine are similar to those in inpatients without pre-existing thyroid dysfunction.
Methods
We conducted a cross-sectional study in patients admitted for non-endocrine reasons to a large tertiary centre between 2007 and 2011. All initial thyroid function tests (TFT) were included in the analysis. Patients with admissions for endocrine reasons and with co-morbidities of hyperthyroidism or thyroid cancer were excluded.
Results
We collected data on 15 710 inpatients with no thyroid dysfunction (TD) and 2240 inpatients treated for hypothyroidism with levothyroxine. The proportions of TFTs, based on the TSH and fT4 results combined, varied significantly between patients on levothyroxine and those with no TD. Only 41.7%(95%CI: 39.7–43.8) levothyroxine-treated patients were biochemically euthyroid (vs. 81.8% with no TD, $P<0.001$), 32.1%(30.2–34.1) had subclinical hypothyroidism (vs. 8.2%, $P<0.001$), 2.0% (1.4–2.6) overt hypothyroidism (vs. 0.2%, $P<0.001$), 7.3%(6.3–8.5%) subclinical hyperthyroidism (vs. 0.2%, $P<0.001$) and 3.4%(2.7–4.2) overt hyperthyroidism (vs. 0.6%, $P<0.001$). Atypical TFT results, not fitting any of the above categories, were found in 13.4%(12.1–14.9) of patients treated with levothyroxine and in 6.7%(6.3–7.1, $P<0.001$) without TD. The mean TSH in those on levothyroxine replacement was 2.68 mIU/l (2.58–2.80) compared with 1.81 mIU/l (1.79–1.83) in those without TD. The difference was statistically significant in univariate ($P<0.001$) and multivariable analysis ($P<0.001$) following correction for sex, age, severity of comorbidities (Charlson Comorbidity Index) and type of admission (elective or acute).
Conclusions
The results of the study highlight the difficulties of achieving good control with levothyroxine in hypothyroid inpatients. It remains unclear if thyroid dysfunction in these patients contributes to the need of hospitalisation and this requires further investigation.

DOI: 10.1530/endoabs.65.P395

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A link between thyroid eye disease (TED) and diabetes?

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Purpose
There are sporadic reports illustrating more severe TED and complications in those with diabetes mellitus (DM) and from local experience these patients have poorer outcomes as seen in other diseases, such as cardiovascular disease. However, the relationship between glycaemia and clinical activity/severity and disease course are not well described.
Methods
A multi-centre retrospective patient-cohort study of 236 patients referred to three TED multidisciplinary (MDT) clinics in London between 2012 and 2019. Patient characteristics were analysed to investigate group-wise differences and correlations between variables collected at baseline to help predict subsequent disease activity, with particular focus being placed on glycaemic control factors.
Results
Median age was 49.0 years (interquartile range: 36–57), 19.5% Asian, 77.5% female. Out of 236 patients, 14.0% had diabetes. The proportion with diabetes also increased with disease activity and severity, culminating in 23.5% in those with dysthyroid optic neuropathy (DON). The median HbA1c in the 131/236 patients who had a baseline HbA1c was 39 mmol/mol (IQR 36–43, NR $<$ 42 mmol/mol). For the whole group, there was a trend towards a positive correlation between HbA1c and CAS ($r = 0.1684$, $P = 0.05$). HbA1c was significantly higher in patients who had moderate-to-severe disease or DON compared to those with milder disease ($P = 0.0114$).
Conclusions
Our results show a higher prevalence of DM compared to the rest of the UK (6.0%) in our cohort with TED. However ethnicity variation, could influence our reported high prevalence. The relationship between HbA1c and disease severity requires further exploration but potentially is a modifiable risk factor that could influence outcome. It is important as therapies for TED e.g. orbital radiotherapy and high-dose corticosteroids are relatively contraindicated in DM. Underlying mechanisms could include aberrant signaling of insulin-like growth factor-I receptor (IGFR-1), as well as low-grade systemic inflammation seen in both disease states.

DOI: 10.1530/endoabs.65.P396

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Thyroid dysfunction in patients with type 1 diabetes: a 10-year retrospective study

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Introduction
Screening patients with type 1 diabetes (T1DM) for other autoimmune diseases such as thyroid disorders has been recommended by international guidelines. Data from the Middle East is currently limited. This study aims to identify the pattern and prevalence of thyroid disorders among the UAE population with T1DM.
Method
A retrospective cohort study was conducted looking at all adult patients (age ≥ 16 years) attending Imperial College London Diabetes Centers in the UAE from 2007 to 2017. All adult patients with T1DM who had thyroid function test done were included. Categorical variable analysis and logistic regression analysis were used to identify factors associated with increased risk of thyroid dysfunction.
Results
Total of 2865 patients with T1DM had thyroid function checked (55% males, mean age 29.7 $\pm$ 11.2 years). Overt hypothyroidism (TSH>10 mIU/ml) was observed in 11.7% of patients and was more common in females (68%). Subclinical hypothyroidism (TSH 4.6 to 10 mIU/ml) was noted in 1.3%, 0.9% had overt hyperthyroidism (TSH <0.01 mIU/ml with elevated serum free T3, T4) and 0.4% had subclinical hyperthyroidism (TSH <0.4 mIU/ml with normal serum free T3, T4). 85.7% had normal thyroid function test result. Total of 430 patients had Thyroid peroxidase antibody (TPO) tested, 52.8% had positive results (≥ 35 IU/ml). Higher prevalence of thyroid dysfunction noted in patients with positive TPO (72.2%) compared to patients with negative TPO (28.6%) (odds ratio 6.2, 95% confidence interval 4.0–9.5, $P<0.001$).
Conclusions
Our results indicate that thyroid dysfunction is common in the UAE population with T1DM. The most frequent thyroid dysfunction was overt hypothyroidism

(11.7%). Assessment of TPO antibodies is valuable in detecting and predicting thyroid dysfunction in patients with T1DM. Our results reinforce the importance of annual screening for thyroid disorder in the UAE population with T1DM.

DOI: 10.1530/endoabs.65.P397

P398

Thyroid function testing in the first trimester of pregnancy – no role for screening?

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Background
Normal maternal thyroid function is essential for optimal fetal neurological development. However, targeted screening for thyroid dysfunction in the first trimester of pregnancy, together with the criteria that should be applied, remains controversial.
Aim
To determine the efficacy of targeted screening for discovering new cases of thyroid dysfunction in pregnancy.
Method
All women who delivered their babies at Imperial College Healthcare NHS Trust between 1/3/17 and 31/12/17 and had thyroid function tests checked during pregnancy were retrospectively reviewed. Criteria for TFT testing include: diabetes; other endocrine disorders; drugs that affect the thyroid; symptoms of thyroid disease (including hyperemesis); family history of thyroid disease. Local reference ranges for 1st trimester include: TSH 0.2–3.6 miU/l and fT4 9.9–15.2 pmol/l.
Results
Thyroid function was checked in 417 women in the first trimester (median TSH 1.14 iU/l, IQR 0.55–1.79 iU/l). Of these women, 157 women had no history of thyroid dysfunction. Recorded reasons for screening included: diabetes including gestational diabetes ($n=51$); other endocrine disorders ($n=5$); hyperemesis ($n=25$); other autoimmune disorder ($n=3$); other ($n=9$). No reason was recorded for 64 women (40.8%). In women without known thyroid dysfunction, no new cases of clinical or subclinical hypothyroidism were detected (median TSH 0.85 iU/l, IQR 0.45–1.38 iU/l). In 17 (10.8%) women, TSH measured <0.3, and of these 10 had a fT4 above the upper limit of the reference range. Nine women with low TSH had documented hyperemesis.
Discussion
In this multi-ethnic cohort, targeted screening identified no new cases of clinical or subclinical hypothyroidism in the 1st trimester. This would argue against testing for hypothyroidism in women without a history of thyroid dysfunction, unless there is a strong suspicion of thyroid disease. Larger numbers are needed to confirm this. Irrespective, clinicians must remain vigilant for cases of hyperthyroidism, especially as the symptoms overlap with those of hyperemesis within the first trimester.

DOI: 10.1530/endoabs.65.P398

P399

Factors involved in the relapse of autoimmune thyrotoxicosis following first line treatment with anti-thyroid medication

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Aim
Anti-thyroid treatment with carbimazole or propylthiouracil is the first-line treatment for autoimmune thyrotoxicosis in the UK. Following 12–18 months treatment there is a significant relapse rate (at least 50%). This study analysed the demographics and clinical features of 100 patients with relapsed thyrotoxicosis to examine which variables are predictive of relapse.
Methods
This retrospective study included adult patients identified using our electronic database of patients seen in thyroid clinic between 1st June 2018 and 1st June 2019. Clinical details and biochemical values obtained from electronic records were analysed using descriptive statistics and logistical regression.
Results
Of 100 patients, 77% were female, with 21 different ethnic origins, predominantly White/British. The average age of first presentation of thyrotoxicosis was 39 years (range 16–78 years). Of those who had TSH-R Ab levels available, 99% were elevated at diagnosis; the concentration of which directly correlated to time interval between relapse ($P = 0.03$; those with the highest concentration relapsing sooner). 46% had documented goitre at initial diagnosis and 9% had documented eye disease. There was also a correlation with duration of first treatment and time interval to relapse ($P = 0.004$, those with shortest duration of treatment relapsed most quickly). 12% relapsed whilst on a low dose anti-thyroid medication (5 mg CBZ or equivalent).
Conclusion
Our study demonstrates a significant correlation between initial TSH-R Ab concentration and duration of initial treatment determining the time interval for relapse. We found no correlation between the presence of goitre and the sample size was too small to assess the relationship with TED. Further research into factors determining relapse in Graves' disease should be established and reliable scoring models need to be developed for predicting relapse in individual patients to guide long-term therapy.

DOI: 10.1530/endoabs.65.P399

P400

An abnormal TSH can persist throughout pregnancy following gestational transient thyrotoxicosis and is not associated with increased maternal or foetal risk: a single centre retrospective cohort study

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Introduction
Gestational transient thyrotoxicosis (GTT) affects 2–3% or pregnancies of European women and 11% of pregnancies of Asian women and typically resolves within the 2nd trimester. GTT rarely manifests with the typical symptoms of thyrotoxicosis and instead is associated with hyperemesis gravidarum. GTT can be confused with thyrotoxicosis occurring in pregnancy which requires prompt treatment with antithyroid drugs (ATDs) to minimise maternal and foetal risk. Injudicious use of ATDs when not required is associated with unnecessary risk to the developing foetus.
Methods
Retrospective cohort study of women attending the antenatal endocrine clinic at Birmingham Heartlands Hospital, UK between 2013 and 2018. Biochemical data and treatment were recorded and clinical outcomes determined by subsequent patient interview post-delivery. Management was compared against British Thyroid Foundation guideline recommendation 3.2 advocating that most women with GTT do not require treatment with ATDs.
Results
Of the 45 patients identified with GTT only 1 was treated with β-blockers and 1 with ATDs. Only 25 patients had normalised TSH (≥ 0.4 mU/l) by the end of the second trimester. 8 patients did not have a detectable TSH till after delivery. There were no incidences of maternal heart failure, foetal loss or low birth weight. 1 patient developed pre-eclampsia requiring C-section and 1 patient had a premature labour.
Conclusions
The majority of our patients did not require ATDs or β-blockers in accordance with published guidance. Maternal and foetal complications did not occur at rates higher than anticipated in pregnancies not complicated by GTT. A low/suppressed TSH persisted later than previously reported though time for

resolution was not associated with increased risk. Informed discussion and careful observation remain the central management strategy in GTT.

DOI: 10.1530/endoabs.65.P400

P401

Management of thyroid disease in pregnancy – a national survey

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Background

Thyroid disease in pregnancy can have a profound impact on both mother and fetus. Guidelines on diagnosis and management are lacking in the UK and there is significant variation between European and US guidelines. This survey aimed to gather data on current management by endocrinologists in Scotland.

Methods

An online survey was created using Google Forms and emailed to endocrinology trainees and consultants in Scotland (April 2019). The survey questioned management of hypothyroidism and Graves' disease in pregnancy. Submissions were anonymised and analysed.

Results

Forty two responses were received (27% target sample response rate) with 86% of all responses from consultants. *Hypothyroidism:* The majority (72%) of endocrinologists elect to treat SCH in pregnancy although there was variation in how this was defined. Only 45% work in centres where trimester-specific TFT ranges are available. *Graves' disease:* 88% recommend women who conceive on carbimazole are switched to PTU in early pregnancy but only 40% recommend switching back to carbimazole in the second trimester. 57% of endocrinologists currently recommend definitive treatment (radioiodine or thyroidectomy) of Graves' disease prior to pregnancy.

Conclusions

This survey demonstrates wide variation in current management of thyroid disease in pregnancy across Scotland. These results highlight the need for cohesive guidelines in the diagnosis and management of thyroid disease in pregnancy.

DOI: 10.1530/endoabs.65.P401

P402

Rates of maternal complications from TRAb positive pregnancies are low, but strongly positive TRAb in later pregnancy is associated with adverse neonatal outcomes

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Introduction

Graves' disease during pregnancy may cause maternal or neonatal complications, including arrhythmia, thyroid storm, congenital anomalies and neonatal thyroid dysfunction (TD). The optimal timing and frequency of TRAb measurement in pregnant women with a history of TD, and whether fetal monitoring could be limited to those with a strongly positive TRAb, is unclear.

Methods

Retrospective case note review of women with elevated TRAb (>1 iU/l) during pregnancy at our institution (2013–2017).

Results

47 women had a positive TRAb and/or received ATDs during pregnancy. 4/47 women with a negative TRAb in the first trimester developed a positive TRAb (highest 4.5 iU/l) later in pregnancy. 10/47 had a strongly positive TRAb (>3 iu/l) in the first trimester, of whom the majority (n8) had a positive TRAb (>1 iu/l) later in pregnancy. Only one mild congenital anomaly was recorded in those on ATDs (all PTU, n19). Neonatal TD occurred in five babies; necessitating temporary treatment with carbimazole (n1) or thyroxine (n1).

Table 1 Neonatal outcomes depending on TRAb level in third trimester.

	TRAb <1 iU/l	TRAb 1-3 iU/l	TRAb >3 iU/l
Number of pregnancies	4	26	17
Number of live births	4	26	17
Fetal thyroid dysfunction	0	0	5
Congenital defects	1 (No ATD)	0	1

Conclusions

Almost all with a strongly positive TRAb in the first trimester have a persistently positive TRAb later in pregnancy. Development of a newly positive TRAb in late pregnancy is rare. No adverse maternal outcome during pregnancy was reported, however neonatal thyroid dysfunction occurred in almost 30% of babies born to women with a strongly positive third trimester TRAb. Our findings suggest that early pregnancy TRAb predicts later TRAb levels; and that screening for fetal thyrotoxicosis should be intensified in women with a strongly positive third trimester TRAb.

DOI: 10.1530/endoabs.65.P402

P403

Iopanoic acid safely, quickly and effectively induces euthyroidism in resistant thyrotoxicosis

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Introduction

Thyrotoxicosis resistant to the usual treatment is rare, but potentially fatal. In such situations, the optimal next treatment is unclear. Iopanoic acid (IA) was historically used as an oral contrast agent; it's capacity to treat thyrotoxicosis has been limited in recent years due to its restricted availability.

Methods

Retrospective case note review of patients treated with IA for resistant thyrotoxicosis at our institution over the past 10 years.

Table 1 Outcome of iopanoic acid treatment in resistant thyrotoxicosis.

	Age, gender, outcome, cause tof hyroid disease	FT4 pmol/l* RR 10-19.8	FT3 pmol/l* RR 3.5-6.5
Case 1	42, F, GD	69, 45	28, 6.4
Case 2	36, F, GD	63, 16	n/a, 4.8
Case 3	37, F, GD	44, 25	n/a, 3.3
Case 4	55, M, AIT	95.6, 38	17.9, 3.3
Case 5	65, M, AIT	85, 72	9.1, 6.6
Case 6	64, M, AIT	64, 48	10.8, 2,.4
Case 7	36, M, AIT	86, 57	21.8, 2.9

*Before, and after, treatment with Iopanoic acid.

Results
7 patients (3 GD, 4 AIT) received IA. Fall in FT4 and FT3 levels was seen in all (Table 1). There were no adverse effects. 6 patients underwent uncomplicated thyroidectomy. One patient (case 5) developed severe multifactorial myopathy (steroids, LMNA mutation, AIT) prior to iopanoic acid administration; he later died of pneumonia.
Conclusion
Iopanoic acid was highly efficacious at rapidly inducing biochemical euthyroidism (normal FT3) in all patients, was well tolerated and enabled safe thyroidectomy. Notably, FT4 remained elevated due to the predominant mechanism of action of inhibition of T4 to T3 conversion. Iopanoic acid is a safe and effective method of restoring euthyroidism in resistant thyrotoxicosis, current availability is limited to laboratory grade; development of a pharmaceutical grade compound would be highly advantageous in urgent or resistant cases of thyrotoxicosis.

DOI: 10.1530/endoabs.65.P403

P404

Thyroid eye disease (TED): patient demographics across three multi-disciplinary (MDT) clinics in London, UK

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Purpose
There is increasing evidence that a multidisciplinary (MDT) approach optimises diagnosis and management in active Thyroid Eye Disease (TED) and is recommended by current TEAMeD-5 guidelines[1]. Here we aim to describe the clinical and endocrine characteristics of a large cohorts of patients with TED seen in 3 MDT clinics in London.
Methods
A retrospective patient-cohort study of 236 patients with suspected TED referred to these services between 2012 and 2019. Whole group correlations and subgroup analyses were analysed at baseline across several patient factors.
Results
Median patient age was 49.0 years, 77.5% were female, 23.3% Afro-Caribbean. 166 (70.3%) were on treatment for Graves' thyrotoxicosis, 25(10.6%) were hypothyroid at first clinic and 29 (12.3%) had normal thyroid function and on no treatment. Of 183 (77.5%) patient who had an autoantibody measurement, 80.5% had positive thyroid-stimulating hormone (TSH) antibody titre, with the median titre being 6.6 IU/l (IQR:2.4–17.8, normal: <1.75 IU/l). A positive correlation between Clinical Activity Score (CAS) and TSH antibody titre was found ($R = 0.30$, $P < 0.05$). There were 52/236 (22.0%) current smokers, all of whom received documented smoking cessation advice. 32.5% patients had a positive family history for thyroid disease, however significantly fewer patients with sight-threatening disease had a positive FH than those without ($P < 0.05$). Patients with sight-threatening disease were significantly older than those without ($P = 0.0378$).
Conclusion
These results suggest that cases of sight-threatening disease were more prevalent in older populations and reported family history was not a predictor of disease activity. TSH R antibody demonstrated a positive correlation CAS but other factors influence the variance seen in CAS. Further biomarkers are warranted in this complex, costly and debilitating disease.

DOI: 10.1530/endoabs.65.P404

P405

Weekly thyroxine administration to aid diagnosis and improve treatment compliance

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Introduction
The thyroxine absorption test (TAT) is well established to investigate persistently raised TSH in patients on L-thyroxine. We review our experience with this test.
Method
Blood was taken for baseline FT4, FT3, TSH measurements and malabsorption screen. A week's supply of L-thyroxine (1.6 mcg/kg$\times$7) was administered orally under direct supervision and FT4 and TSH measured 2 h later. Patients continued on the same weekly dose for 4 weeks and increased, if TSH still elevated, to 2 mcg/kg$\times$7 for 2 weeks; thereafter the total dose was given in two divided doses, twice weekly. Absorption was considered adequate if FT4 increased by >50% compared to baseline value at 2 h. FT4 and TSH were measured by chemiluminescence on an Abbot analyser. TFT data was collected at $\geq$6 months following the test to review compliance.
Results
Twenty four patients (4 male, 20 female) with a mean (range) age of 36 (16–74) years, and weight (range) 86 (47–124) kg underwent TAT. Prior to testing, the mean daily L-thyroxine dose was 222 (range: 75–375 (g/day). Adequate L-thyroxine absorption was demonstrated in 96% patients. In 71% of patients, TSH values normalised after 4–6 weeks confirming poor compliance. Seven patients failed to suppress TSH at the end of 4–6 weeks; one patient was on dialysis and TSH normalised following renal transplantation; three required 2.0$\times$weight (kg)$\times$7 g once weekly and a further three required higher dose split as twice weekly. By six months, TSH values were maintained in range or suppressed (as needed in high risk thyroid cancer) in 85% patients.
Conclusion
TAT is useful where non-compliance or malabsorption is suspected. Furthermore, based on the response, a treatment plan can be implemented using once or twice weekly dosing which can improve compliance and treatment outcomes.

DOI: 10.1530/endoabs.65.P405

P406

Radioiodine therapy for Grave's disease: does post treatment block and replace therapy reduce the incidence of biochemical hypothyroidism?

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Prior to therapy, patients choosing I131 therapy for the treatment of Grave's disease were pre treated with carbimazole. Post I131 they have their thyroid function checked monthly in primary care prior to clinic review at 3 months. Carbimazole can be restarted if clinically indicated and treatment with thyroxine was recommended if their TSH was greater than 3.5 mU/l (ref range 0.35–5.5). A previous audit had demonstrated that 24% of patients had an elevated TSH greater than 5.5 mU/l on more than one occasion prior to commenting thyroxine. In 2016 a number of the endocrinologists started using block and replace (B&R) prior to I131. B&R was discontinued 7 days prior to treatment and recommenced 7 days after treatment. Carbimazole was discontinued at 6 months and thyroxine continued lifelong if indicated. We reviewed the last 2 years outcome data to determine if there was a difference in post treatment hypothyroidism (defined as TSH>5.5 mU/l at 6 months) or relapse rate. (Defined as treatment with carbimazole at 12 months post therapy). Since 2016, fifty seven patients have been treated for Graves's disease of which 22 used B&R and 35 standard carbimazole pre-treatment. TSH >5.5 mU/l at 6 months in the carbimazole and B&R groups were 34% and 18% respectively and relapse rate at 12 months 17% and 9%. Thus, B&R post I131 therapy resulted in a similar cure rate and was less likely to result in an elevated TSH at 6 months.

DOI: 10.1530/endoabs.65.P406

P407

Fixed 600 Mbq radioiodine activity is more effective than variable dose in treatment of benign thyroid disease

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Purpose

To compare effectiveness of different radioiodine activities used for the treatment of benign thyroid disease.

Method

We retrospectively reviewed our local radioiodine audit data collected over 7 years duration. Patients with benign thyroid disease and known post-treatment biochemical outcomes were included. Data were analysed for primary diagnosis, activity dose, and biochemical outcomes in 6 and 12 months post-treatment.

Results

Over period of 7 years 276 patients received radioiodine therapy as primary or secondary treatment for benign thyroid disease. 249 of those have both radioiodine activity and biochemical outcomes known at the time of the study. Mean age was 54 years and 80% were females. Main indication for treatment was Hyperthyroidism (93%) of which 56% were Grave's disease. Activity distribution was comparable with 46% of patients receiving 600 Mbq, 39% had 400 Mbq, and only 15% of other activities (500 or 800 Mbqs). Overall cure rate measured as the number of patients achieving euthyroidism or hypothyroidism post radioiodine therapy, was 88% in six months and 89.5% at 12 months. When divided in to the two main activities; cure rate was 83.5% at 6 months for 400 Mbq, which remained the same at 12 months follow up. For 600 Mbq, the cure rate was 94% at six months with further improvement to 96% at 12 months. There was no significant between group's difference in pre-treatment antithyroid drug therapy, primary or secondary indication for treatment, duration of ATD withdrawal prior to radioiodine therapy, goitre size or smoking status.

Conclusion

On this sizable sample, fixed radioiodine activity of 600 Mbqs for the treatment of hyperthyroidism, was more effective than variable dose in achieving biochemical cure (96% compared to 83.5%). This finding was independent of the primary hyperthyroid pathology, pre-treatment with anti-thyroid drug therapy or goitre size.

DOI: 10.1530/endoabs.65.P407

P408

Weight trajectory during treatment for hyperthyroidism

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Objectives

Hyperthyroidism is associated with a high basal metabolic rate and weight loss is a common symptom. However, it has been observed, that once patients are treated, they gain back the lost weight and may also put on more. Given that weight gain is a health factor, there's interest in studying the effect that the thyroid levels have on weight gain and potential harmful health consequences.

Methods

79 patients (58 female) with hyperthyroidism from thyroid clinic at the University Hospital of Wales were recruited. The mean age was 53 years, IQR 43-67. Premorbid weights and their changes during follow-up (max 24 months) were recorded. Participants were stratified by age and sex. The program STATA was used to apply the Wilcoxon signed-rank test.

Results

At month 0, body weight (mean $\pm$ S.D.) was 74.7 kg $\pm$ 2.10. During the first 3 months of treatment, there wasn't a significant increase in body weight, but as the time went by, the mean highest weight recorded was 77.8 ± 2.18, which was significantly higher than the baseline weight: $P < 0.0001$.

Conclusion

The data obtained follows what is already known in literature, which is that there is weight gain during treatment for hyperthyroidism. However, in this clinic population, the mean increase in weight was 3.1 kg. Assessment of body composition would be of value to measure the different body components (bone mass, muscle mass and fat mass) and determine what caused the increase in weight. The weight gain is not excessive, so focus interventions such as the involvement of dieticians may not be cost effective. Larger studies are needed to investigate whether different treatments modalities influence weight gain and whether those patients who become hypothyroid during treatment could also have substantially increased risk of excessive weight gain.

DOI: 10.1530/endoabs.65.P408

P409

Patients with hypothyroidism of differing aetiologies are often inadequately treated without appropriate dose adjustment: a retrospective cohort study based in primary and secondary care

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Introduction

Primary hypothyroidism is most commonly caused by autoimmune hypothyroidism whilst additional causes include post radioactive iodine treatment (RAI) whereas central hypothyroidism is typically associated with pituitary disease. Treatment in primary hypothyroidism aims to maintain the TSH within the reference range whilst treatment of central hypothyroidism is aimed at maintaining free T_4 in the upper half of the reference range as established by international guidance. Despite clear guidance patients are at risk of over or under treatment.

Methods

Adults with autoimmune hypothyroidism were identified from a primary care registry whilst those with post RAI or central hypothyroidism were identified from within the relevant outpatient cohorts of Birmingham Heartlands Hospital. Patients were included if they were receiving levothyroxine and had been reviewed by a clinician between October 2016 and September 2017. As such 64 patients with autoimmune hypothyroidism, 63 patients with post RAI hypothyroidism and 38 patients with central hypothyroidism were identified. Their thyroid function tests and any subsequent treatment adjustment were recorded.

Results

Adequate treatment rates were lower than anticipated (25% under treated, 9% over and 66% adequate in autoimmune hypothyroidism; 21% under, 5% over and 74% adequate in the post RAI hypothyroidism; 52% under, 3% over and 45% adequate in the central hypothyroidism group). Dose adjustment in under treated patients occurred variably (14% in the autoimmune hypothyroidism group, 81% in the post-radioiodine hypothyroidism group, and 24% in the central hypothyroidism group).

Conclusion

In this retrospective cohort study, all groups contained patients that were inadequately treated for their hypothyroidism. Under treatment was more common than over treatment and was especially common in patients with central hypothyroidism who despite being reviewed in a specialist centre often did not have appropriate dose adjustment.

DOI: 10.1530/endoabs.65.P409

P410

Simultaneous occurrence of Graves' disease in a monozygotic twin with type 1 diabetes

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Graves' disease is an autoimmune disorder of the thyroid gland. Patients with type 1 diabetes (T1DM) are at a higher risk of developing autoimmune diseases including thyroid disorders. To our knowledge, diagnosing Graves' disease at the same time in a monozygotic twin with T1DM is a rare occurrence. We present a case of monozygotic female twin with T1DM, who both developed Graves' disease at the same time. Type 1 diabetes was diagnosed in one of the twins (twin A) at the age of 10, 4 years later her sister developed type 1 diabetes at age of 14 years (twin B). They lived in the same house and went to same school and college. Both patients and their parents are nonsmokers. There has been no family

history of autoimmune diseases or thyroid disorders. Four years before the diagnoses of Graves' disease, Twin A was diagnosed to have autoimmune hypothyroidism while her sister (twin B) was noted to have a very high titre of TPO antibodies with evidence of subclinical hyperthyroidism which was managed conservatively. Treatment with thyroxine replacement was initiated for twin A lasting for 48 months, which was eventually terminated when both twins started to demonstrate clinical and biochemical features of hyperthyroidism at the same time. Graves' orbitopathy was not present. Biochemical assays confirmed the diagnosis of Graves' disease. Both patients had positive thyroid receptor antibodies (TRAb) which was negative 4 years earlier. Both patients were started on Carbimazole (CM) 15 mg daily. Following one year of treatment with CM, the 2 sisters were clinically and biochemically euthyroidal. This case report supports the hypothesis that genetic factors play an important role in the etiology of thyroid autoimmune diseases and may determine the time window of emergence of the thyroid autoimmunity.

DOI: 10.1530/endoabs.65.P410

P411

Levothyroxine dosage in hypothyroid pregnancies – our experience in a tertiary care hospital T Balafshan, T S Purewal, E Finch, A Tang, D Kalathil Royal Liverpool and Broadgreen University Hospitals NHS Trust, Liverpool Women's NHS Foundation Trust

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Background
Severe maternal hypothyroidism during pregnancy may be associated with delayed development and lower IQ in the foetus. BES (2007) and NICE (2011) guidelines recommend maintaining TSH < 2.5 mU/l with monitoring of maternal thyroid function test (TFT) 4 weekly, especially in the first trimester.
Aim and methods
A retrospective study on all pregnant women with established hypothyroidism attending the Joint Antenatal Clinic (JANC) at Liverpool Women's Hospital from April 2017 to March 2018, using data from online medical records and GP's referral letters.
Result
77 patients attended. 37 (48.6%) had TFTs checked in the 6 month period prior to conception. 46% of these had TFTs within the normal range for pregnant women (TSH < 2.5 mU/l). Of these, 39% developed TSH >2.5 mU/l once they had conceived. Post conception, 34.2% (of 77) had not had TFTs checked till their review at JANC. In 52% (of 77), TSH was not in the recommended range for pregnancy at the 1st TFT check. Of those with TSH outside the recommended range, 76.7% (43.4% of whole cohort) required adjustment of Levothyroxine dose at 1st JANC visit. 87% of the whole cohort required dose adjustment at least once during pregnancy. The average increase in dose was 55% (range 17–400%). TFTs were checked on average 5 times during pregnancy, with average gestation of 32 weeks. The newer American Thyroid Association guideline (2017) recommends TSH < 4 mU/l during pregnancy. Based on that we would have needed to adjust the dose of levothyroxine preconception and on the first JANC visit in 54.5% and 37% of patients ($n = 77$) respectively.
Conclusion
A significant proportion of pregnant women with hypothyroidism require alteration of thyroid medication during pre during and post pregnancy. This increasing workload is best undertaken by assessment in a joint clinic, and subsequent telephone follow up.

DOI: 10.1530/endoabs.65.P411

P412

Health utility of people with treatment-resistant hypothyroidism as measured with the EQ-5D-5L quality of life questionnaire

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Background
Primary hypothyroidism affects about 3% of the general population (5.1% women and 0.9% men). The majority of people are treated adequately with levothyroxine. However about 5–10% of hypothyroid patients (representing between 75 000 and 150 000 adults in the UK) continue to experience profound and sometimes disabling symptoms, such as fatigue/depression/impaired cognition, in spite of being adequately replaced biochemically. Before any trial of alternatives to levothyroxine (eg natural desiccated thyroid (NDT)) it is important to evaluate the appropriateness of health outcome measures, estimate how patient self-reported outcomes compare with other chronic disorders, and assess variability in response to inform sample size calculations.
Methods
Individuals were recruited with the help of Thyroid UK. All were judged to be clinically resistant to levothyroxine despite being biochemically euthyroid (TSH within laboratory reference range). They were invited to complete on-line a validated multi-attribute health utility instrument, the EuroQol EQ-5D-5L questionnaire and accompanying EQ-VAS (visual analogue scale. EQ-5D-5L index values (utilities, a preference-weighted measure of patients' health valuation) were estimated based on the EQ-5D-5L cross walk value set for the UK.
Results
Responses were available from 31 people. Mean (S.D., min, max) EQ-5D-5L utility was 0.54 (0.23, 0.00, 0.84); and EQ-VAS was 49.4 (16.2, 10.0, 80.0). 26/31 (84%) individuals reported having moderate problems in at least one attribute, most often their ability to perform usual activities, and anxiety or depression; 10/31 (32%) reported severe problems; and 4/31 (13%) reported extreme problems.
Conclusion
As the first assessment of EQ-5D-5L utilities in this patient group, our findings provide a basis for powering a trial of alternative treatment options to levothyroxine. Reported health utilities in these individuals are comparable to those reported by patients with lung cancer, or acute cerebrovascular disease and would rank in the bottom decile of 100 chronic diseases.

DOI: 10.1530/endoabs.65.P412

P413

A prospective clinical trial on the efficacy of lithium as adjuvant therapy to radioiodine in the treatment of hyperthyroidism (RAILIT study)

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Background
Radioactive Iodine (RAI) is one of the main treatment modalities of hyperthyroidism. Its success rate seems to differs. Lithium efficacy as adjuvant therapy to RAI remains debatable.
Objective
To assess the efficacy and safety of lithium carbonate as an adjuvant therapy to RAI in the treatment of hyperthyroidism.
Methods
This is 24 weeks prospective study carried out in the Endocrinology Unit, Penang General Hospital. Lithium carbonate 300 mg twice daily for fourteen days starting on the day of RAI therapy. Lithium carbonate 300 mg twice daily was given on the day of RAI (at least 2 h prior to RAI) to 40 subjects and no added medication in the control group. Subjects were followed up with 6 study visits to assess side-effects,compliance to medication, determining cure with adjustments to medications by the study doctors.
Results
There were no significant difference in the clinical, demographic and biochemical profile of the two groups. Dose of RAI standardized to 15 mCi in both groups. The cure rate in RAI plus lithium group was 62.2% vs 63.2% ($P = 0.932$) in control. Mean time to cure in RAI plus Lithium versus RAI alone group were similar 13.6 ± 6.1 weeks vs 13.2 ± 6.5 weeks ($P = 0.841$). There was numerically higher cure rate in Toxic Multinodular goitre in the RAI plus lithium group 10 out of 14 (71.3%) versus RAI alone group 8 out of 15 (53.3%)($P = 0.316$) though this was not statistically significant. Lithium however was able to prevent thyroid hormone surge 2 weeks post RAI as the median Free T4 was lower at week 2 post RAI compared to baseline ($P = 0.004$).

Conclusion
Lithium carbonate does not improve the efficacy of RAI in hyperthyroid patients. Its role in improving efficacy of RAI in toxic multinodular goiter and prevention of thyroid hormone surge post RAI need further investigations.

DOI: 10.1530/endoabs.65.P413

P414

Place of elastography in the diagnostic of intermediary cytology thyroid nodules

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Introduction
Intermediate cytology comprises unclear result form Bethesda III and IV category. This category is still present in the general results of thyroid cytology, with 2–18% AUS/FLUS and 2–5% FN. The attitude after such a results is not standardize, follow up, lobectomy or thyroidectomy being the possible indications to solve such a case. The current paper presents the value of predictive value of ultrasound techniques in the final judgment of these cases.
Methods
Elastography is incorporated in some current used models for thyroid nodules risk stratification; high stiffness is considered a risk factor. Our Center uses Russ's risk stratification model, using high stiffness as the 6th risk criteria, besides hipoecogenicity, homogeneity, margins, shape and calcifications, using a Hitachi Preirus machine, with a 5 cm wide multifrequency linear probe, equipped with strain elastography technique.
Results
Study evaluated the FNAC results from 2017 to 2018: comprising 52 cases with intermediate cytology results: 31 AUS, 14 FLUS, 7 FN. In the FLUS/AFLUS cases (45 cases), cancer was confirmed 13 cases, respectively 6 cases with borderline follicular neoplasia, 17 of these cases being classified as high risk on ultrasound. The 26 benign cases were classified as low risk (8 cases) and intermediate US risk (18 cases). In the FN group, 4 cases where identified as cancer, 3 as benign. The diagnostic quality was Sensitivity of 30% with a very high specificity of 89.5 (for FLUS /AFLUS case) respectively sensitivity of 25% with a excellent specificity of 100% for FN cases. High-risk cases, are suggestive for malignancy, both in AUS/FLUS and FN cytology reports.
Conclusion
The ultrasound analysis of nodules with intermediate cytology identifies the vast majority of cancer cases. High-risk category, defined as conventional high risk and increased stiffness identify the vast majority of cancers in intermediate cytology group.

DOI: 10.1530/endoabs.65.P414

P415

Thyroid dysfunction in adult hematopoietic stem cell transplant patients treated with Alemtuzumab based conditioning

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Objective
To study the effect of alemtuzumab used in Reduced Intensity Conditioning prior to hematopoietic stem cell transplant (HSCT) on thyroid function.
Methods
This retrospective case review of 13 patients (9 male, 4 female) who underwent HSCT and had alemtuzumab based conditioning regimen. 5 patients had Acute lymphoblastic leukaemia, 3 severe a plastic anaemia, 1 acute myeloid leukaemia, 1 congenital bone marrow failure, 1 chronic granulomatous disease (GCD) 1 juvenile myelomonocytic leukaemia. Treatment age mean 7.6 years (range 1–17); mean age at follow up: 14.6 (Range: 8–18). 7 patients had Total body Irradiation (TBI) (dose 14.4 Gy), 1 had additional Cranial RT (3 Gy). The cumulative dose of alemtuzumab used was 1 mg/kg.
Results
Ten patients had TFT done post HSCT. 8 had normal thyroid function whereas 2 patients were on thyroxine replacement (25–125 mg a day), antibody status unknown. None of the patient had thyrotoxicosis.1 TBI patient had papillary carcinoma, treated with surgery and RAI.
Discussion
Alemtuzumab is recombinant humanized IgG monoclonal antibody which depletes CD52+ cells used to in HSCT to reduce rate of graft versus host disease. 41% of patients with Multiple Sclerosis treated with alemtuzumab developed thyroid dysfunction with Graves (72%) being the most frequent thyroid disorder[(1).] In this small case review, this does not appear to be common phenomenon in patients receiving alemtuzumab before HSCT. The mechanism of alemtuzumab-induced autoimmunity has been attributed to a breakdown in self-tolerance during immune reconstitution[(2)] and differential lymphocyte reconstitution causing early hyper-repopulation of immature B lymphocytes[(3).] HCST may affect this immune reconstitution process. Or differences may be attributed to a dose effect. Thyroxine in this cohort is often started when TSH is within the normal range so diagnosis of hypothyroidism is not confirmed. We are currently looking at effect of alemtuzumab on thyroid function in a larger cohort.

DOI: 10.1530/endoabs.65.P415

P416

Outcomes of Liraglutide as treatment for weight regain after bariatric surgery: A 2-year retrospective study

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Introduction
Limited data is available on Liraglutide as a treatment option for weight regain after bariatric surgery. We aim to report the efficacy of Liraglutide as a treatment for weight regain in UAE population who underwent bariatric surgery.
Methods
Retrospective analysis was performed on all patients with weight regain after bariatric surgery who received Liraglutide (dose range 0.6 up to 3.0 mg/day) while attending bariatric clinic of Sheikh Khalifa Medical City (AD, UAE) over two years from 2017 to 2019.
Results
56 patients who received Liraglutide for weight regain after bariatric surgery during the study period were identified. 49 patients were included for final analysis as 7 patients stopped Liraglutide (5 due to severe nausea and vomiting and 2 due to pregnancy). Mean age was 37.9 ± 9.1 years and majority of patients were female (81.6%). 59.2% had Laparoscopic sleeve gastrectomy (LSG $n=29$), 36.7% had laparoscopic Roux-en-Y gastric bypass (LRYGB, $n=18$) and 4.1% had Laparoscopic gastric banding ($n=2$). Mean presurgical weight was 123.2 ± 17.8 kg and mean BMI was 58.4 ± 10.2 kg/m^2. Mean minimal body mass index after surgical intervention was 33.5 ± 5.1 kg/m^2 and mean weight was 85.7 ± 12.9 kg. Mean weight at Liraglutide initiation was 95.1 ± 13.3 kg and mean BMI of 36.9 ± 4.4 kg/m^2. After 3 months, mean weight and BMI reduction were 5.4 ± 9.8 kg and 1.3 ± 1.1 kg/m^2 respectively ($P<0.01$).
Conclusion
Liraglutide can be considered as a safe and effective adjunctive treatment for weight regain after bariatric surgery. Further studies are required to identify clinical predictors that could affect the response to Liraglutide in these patients.

DOI: 10.1530/endoabs.65.P416

P417

An audit of the use of liothyronine (LT3) in the East Sussex Health Care Trust

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Context
NICE and BTA agrees that combination L T4 and LT3 can be used in patients with symptoms persisting after adequate use of LT4.
Methods
We retrospectively audited the patients coming to the endocrine clinics of ESHT whether they followed the local agreed protocol of LT3 usage. We checked if they had:
1. Initiation of LT4 by an endocrine specialist.
2. If other causes of tiredness were ruled out.
3. If LT4 doses were adequately decreased on starting LT3.
4. If they were on combination therapy or just LT3.
We also looked at symptoms that caused them to be put on LT3 and whether they improved. We also looked at the levels of TSH, fT4 and fT3 before and after initiation of LT3.
Results

12 patients who used T3 were studied. 9 patients were still on it.
8/12 (67%)of T3 initiation was by consultants, 2/12(16%) was by Gps, 1 was unknown and 1 was over the counter.
All patients noticed improvement in symptoms after starting T3 and wanted to continue.
5/12 (42%) had appropriate reduction in LT4 on initiation of LT3. 7/12, (58%) didn't.
11/12 (92%) had other causes of fatigue ruled out.
7/12 (58%) were overreplaced even before T3 initiation, but symptomatic.
2/12 (16%) were undereplaced and 3/12 (25%) had normal TFTs.
The overreplaced patients remained with suppressed TSH after T3 start.
8/12 (67%) had suppressed TSH after combination therapy. 4/12 (33%) had normal TFTs.
3 patients came off T3 treatment; 2 because their CCG wouldn't prescribe and one had cardiac morbidity.

Conclusions
Stricter adherence to guidelines on initiation of LT3 is required. Overreplacement and suppression of TSH is a risk. Patients felt symptom relief and most wanted to stay on the combination treatment.
DOI: 10.1530/endoabs.65.P417

P418

'Toxic adenoma; biopsy or not to biopsy?'
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Toxic adenomas nodules rarely harbour cancer. Fine needle aspiration (FNA) is often not done due to the rarity of these lesions being cancer, the difficulty in interpreting cytology in hyperthyroid patients and the rarely reported instance of precipitating thyrotoxicosis. Here, we present two young Caucasian female patients with toxic adenomas, who underwent hemithyroidectomy and the histology unexpectedly revealed differentiated follicular cancer. The first is a 29-year-old patient who was incidentally found to have a 46 mm left thyroid nodule (U3). She had no other risk factors for thyroid cancer. The biochemistry was consistent with thyrotoxicosis following which she was commenced on carbimazole. The patient opted to have surgery and underwent left hemithyroidectomy when she was euthyroid. The histology confirmed fully excised minimally invasive follicular cancer with capsular and lymphovascular invasion (pT2R0). The second is a 13-year-old patient, who was referred to endocrinology with T3 toxicosis. On assessment, she was found to have a large (46 mm) left sided thyroid nodule, which the patient and family were previously unaware of. Once, she was rendered euthyroid with carbimazole, it was decided to surgical excise the adenoma (hemithyroidectomy). Even though the ultrasound had initially shown benign features of the nodule (U2), the histology revealed minimally invasive follicular cancer (pT2R0) with capsular but no vascular invasion. We suggest that while thyroid cancer is rare in patients with toxic adenomas, this should be considered among the differentials especially if there are risk factors for cancer, or suspicious features on ultrasound imaging. A review of literature shows that compared to adenomas in euthyroid patients, patients in this group are generally younger and predominately female. If an FNA is considered, it should only be performed when the patient is euthyroid.
DOI: 10.1530/endoabs.65.P418

P419

Postoperative hypoparathyroidism in patients after total thyroidectomy – experience of a tertiary center in Romania
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Objectives
Post-surgical hypoparathyroidism (PoSH) is a common long-term complication after thyroid surgery. The reported median incidence rates of temporary and permanent PoSH was 27% and 1% respectively.
Methods and results
We retrospectively analyzed the files of 552 patients who underwent thyroidectomy in our surgery department between 2015 and 2017 with the aim to assess the prevalence of PoSH and to identify patient and disease related factors associated with postoperative hypocalcemia.
Results
171 (30.97%) patients [153 women (89.5%), median(IQR) age 49(22) years] developed PoSH (88.37% transient). The median(IQR) duration of postoperative hypocalcemia was 60 (67.5) days. Compared to 39 age and sex matched patients without PoSH, patients with PoSH presented the same prevalence of thyroid pathology that recommended thyroidectomy: multinodular goiter 55.6% vs 46.2%, Graves' disease 12.9% vs 17.9%, thyroid carcinoma 31.6% vs 35.9% ($P=0.52$). Preoperative biological parameters (calcemia, PTH, 25-hydroxy-vitamine D, phosphatemia, alkaline phosphatase, creatinine, TSH, FT4, TPOAb) were the same in both groups; yet, median(IQR) magnesemia was significantly higher in PoSH group [2.04(0.17) vs. 1.89(0.28) mg/dl, $P=0.005$]. Preoperative ultrasound characteristics, surgical protocols and pathological data were similar in the two groups. The patients with thyroid cancer that developed PoSH compared to controls had a longer median duration of thyroid surgery [135(60) vs. 110(43) min, $P=0.02$]. In patients with PoSH, median postoperative calcemia was significantly higher in patients with reported difficult surgery [8.2(0.2) vs. 7.9(0.6) mg/dl, $P=0.043$] and the mean calcemia decrease was higher in patients with cervical neck dissection and lymphadenectomy (1.94 ± 0.59 vs. 1.68 ± 0.56 mg/dl, $P=0.033$).
Conclusions
Our data show a high prevalence of PoSH that is likely to increase given the rising number of thyroid surgeries being performed. Further research is needed in order to better define this condition, to establish appropriate treatment and preventive measures.
DOI: 10.1530/endoabs.65.P419

P420

Achievement and maintenance of euthyroidism in patients with Graves' disease: How well do we do?
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Background and aims
Patients with Graves' disease should be rendered euthyroid rapidly and euthyroidism subsequently maintained. Studies have shown this can be achieved at 3 months and maintained for the following 9 months in 90% of patients. The aim of this review was to ascertain whether we were achieving this target within our hospital setting.

Method
We undertook a retrospective analysis of patients with Graves' thyrotoxicosis referred to Royal Bournemouth Hospital. Thyroid function test results (TFTs) from referral to 54 weeks were assessed for frequency of testing and thyroid status at 3, 6, 9 and 12 months.
Results
39 patients with incident Graves' thyrotoxicosis (clinical goitre, thyroid orbitopathy or positive TRAb) who presented between 1 January 2015 and 31 December 2016 and were treated with anti-thyroid medication were assessed. Age 47.7 years (range 19–89), 2 male. 3 patients were lost to follow-up and were excluded from analysis beyond 3 months. 18/39 (49%) patients had TFTs 6 weekly for the first 3 months and 28/36 (78%) had TFTs every 3 months for the following 9 months.
Summary
- Our real-world data achieved euthyroidism in 70% of our patients by 6 months and this was maintained to 12 months.
- A nurse-led rapid-access thyrotoxicosis service is being trialled to facilitate more intense early intervention.

Table 1 Proportion of patients with thyrotoxic, euthyroid or hypothyroid results at time-points ± 2 weeks from referral

Time from referral	3 months	6 months	9 months	12 months
Euthyroid	40%	70%	89%	92%
Thyrotoxic	52%	19%	11%	8%
Hypothyroid	8%	11%	0%	0%
Number of patients	25	27	28	12

DOI: 10.1530/endoabs.65.P420

P421

Analysis of the outcome of repeat Fine Needle Aspiration Cytology for Thy3a thyroid nodules – a retrospective study of 4 year data in a district general hospital

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Introduction
Thy3 classification was subdivided into Thy3a and Thy3f to reduce the dilemma and confusion surrounding the management of patients with indeterminate thyroid nodules. Thy3a lesions are often downgraded or upgraded on repeat sampling and in thyroid MDT.
Patients and method
A retrospective analysis of the patients who had thy3a diagnosis from January 2015 until December 2018 was recorded. All patients who underwent a second sampling were included whereas patients who did not have complete data and private patients were excluded.
Results
Of 54 patients with Thy3a results, 43 were included in the study (6 males, 37 females). Of these, 17 patients underwent a second FNA (39.5%). Eight of these seventeen patients (47%) were downgraded to thy2 on repeat FNA. Of these 4 (50%) did not proceed to surgery and were discharged whereas 4 (50%) who proceeded with surgery had a benign final histology.
Conclusion
Thy3a results do have a moderate risk of malignancy but repeat sampling as shown in our analysis does show evidence of the need to carefully interpret the first sampling outcome and need to consider repeat FNA or MDT discussion to avoid unnecessary surgery for a benign lesion.

DOI: 10.1530/endoabs.65.P421

P422

Propylthiouracil causing pulmonary haemorrhage and glomerulonephritis

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27 years old lady with recurrent Graves' thyrotoxicosis for 5 years delivered her baby uneventfully and her thyrotoxicosis worsened 2 months after pregnancy when her FT4 bounced back up to 38 pmol/l (12–22) so her propylthiouracil (PTU) was increased from 200 to 400 mg. Despite of continuing high dose of PTU for few months she remained thyrotoxic and became neutropenic [Neutrophil 0.67×10^9 (2–7)], decision was made to proceed with thyroidectomy but she developed symptoms of bilateral red eyes, generalised malaise and joint pain. She was noted to have inflammatory arthritis, acute kidney injury [creatinine 153 μmol/l (45–84) with 3+ proteins in her urine dipstick] and new anaemia [haemoglobin Hb 69 g/l (115–165). Autoimmune screen revealed pANCA pattern titre>1:40, anti PR3 56 U/ml (0–2) and anti MPO 67 U/ml (0–3.5), other autoimmune screen including glomerular basement membrane antibodies were negative. CT chest showed basal changes consistent with pulmonary haemorrhage. She was given diagnosis of PTU induced ANCA positive vasculitis with severe pulmonary haemorrhage (causing significant drop in her Hb) and crescentic glomerulonephritis (confirmed on renal biopsy). Her PTU was stopped. She received pulsed steroid followed by weaning steroid course along with Rituximab under close monitoring of rheumatology and nephrology teams. She had blood transfusion. Two weeks after Rituximab therapy she developed hypothyroidism needing a month of Levothyroxine which was stopped as she became euthyroid. She also developed steroid induced diabetes which was treated with gliclazide. As her vasculitis improved, she was referred to ENT for thyroidectomy with the concern about recurrence of thyrotoxicosis. US of thyroid showed slightly enlarged thyroid with no nodules. PTU induced ANCA positive vasculitis is a rare side effect and present wide range of clinical manifestations from mild form with rash or arthralgia to severe with pulmonary and renal involvement. It can be life threatening if remain unrecognised and untreated.

DOI: 10.1530/endoabs.65.P422

P423

Thyrotoxicosis and post RAI hypothyroidism in someone with thyroid hormone resistance: A conundrum

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Introduction
Thyroid Hormone Resistance (THR) is a rare disorder caused by mutations of Thyroid Hormone Receptor characterised by insensitivity of target tissues to thyroid hormone actions. Patients can present with hyperthyroidism or hypothyroidism symptoms.
Case report
49 year lady with recurrent thyrotoxicosis with goitre (1989/1994/1998) treated elsewhere with CBZ/PTU and RAI (2001). She developed post-RAI hypothyroidism and at presentation to our OPD (2015) she was on levothyroxine 100 mcg daily. Abnormally raised TSH levels were noted since 2011 despite normal or elevated FT4 levels. Two representative readings are given.

	13 July 2011	20 October 2015	
TSH	15.7 mU/l	7.9 mU/l	Normal range: 0.27–4.2
FT4	21.4 pmol/l	31.4 pmol/l	Normal range: 12–22

A possibility of THR, TSH-oma or assay interference was considered. Pituitary MRI (15 December 2016) showed no microadenoma. Assay interference was ruled out as there was good agreement between DELFIA and Roche in respect of TSH and FT4. Bloods (21 January 2016): TSH 11.2 mU/l, FT428.5 pmol/l, SHBG 61 nmol/l (32.4–128), Alpha subunit peptide 0.8 IU/l (0–1), TRAB <1.0 U/l (1–1.8). Levothyroxine dose was gradually reduced and stopped over months. TRH stimulation test organized 6 weeks after stopping levothyroxine (13 April 2017) showed a preserved TSH response with basal TSH of 28 mU/l and peak TSH of >100 mU/l. THR can often be misdiagnosed as Graves' disease. THR and Graves can rarely coexist. She was referred to Addenbrooke's where in THRB gene sequencing she was heterozygous for THR beta mutation c.1313G>A, p. (Arg438 His) confirming thyroid hormone resistance. Most THR run in families. However, no family history of thyroid illness was noted in our case. As a child, our patient was hyperactive and currently she is having anxiety with depression. We found that there are multiple family members with hyperactivity and anxiety. We lost follow up after the genetic diagnosis was made.
Conclusion
Correct diagnosis of THR, which requires a high index of suspicion, can avoid unnecessary interventions.

DOI: 10.1530/endoabs.65.P423

P424

Clustering of papillary thyroid carcinoma, familial hypocalciuric hypercalcemia and parathyroid adenoma in members of the same family–Case report

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We report a case of familial clustering of familial hypocalciuric hypercalcemia (FHH) associated with and papillary thyroid carcinoma (PTC). The first presentation in our clinic of one of the patients, female patient, was for severe hypercalcemia. The diagnostic workout for hypercalcemia revealed primary hyperparathyroidism (PHPT) due to a left inferior parathyroid adenoma and undergo surgery. The pathologic report described closely packed chief cells arranged in uniform sheets and cords confirmatory for parathyroid adenoma of left inferior gland. The persistence of the mild hypercalcemia following parathyroid surgery with low urinary Calcium excretion meets the criteria for FHH. We diagnosed her brother with FHH due to asymptomatic mildly elevated serum calcium levels with inappropriate parathormone levels and low urinary calcium excretion. The thyroid ultrasound showed in both patients, solitary thyroid nodules, diagnosed as papillary carcinoma by fine needle aspiration biopsy. Total thyroidectomy with central and lateral compartment lymphadenectomy was carried out. The pathologic report confirms multifocal classical variant of papillary carcinoma, without oxyphilia, with lymphatic and capsular invasion and lymph node metastases in both patients. Both patients received iodine ablation. The association of nonmedullary thyroid cancer, parathyroid adenoma and FHH is a rare occurrence. Further, familial papillary carcinoma is described as part of a few familial tumour syndromes. The familial PTC cases could have more aggressive clinical behaviour than the sporadic ones, as indicated in some series. Even our subjects don't meet the criteria for familial cancer, the unusual occurrence of nonmedullary thyroid carcinoma and FHH, with an affected member of parathyroid adenoma is the first described report. Close surveillance to monitor the thyroid cancer recurrence, the occurrence of new parathyroid adenoma, screening for solid tumours described in familial tumour syndromes associated with familial PTC and the genetic analysis is the future case management.

DOI: 10.1530/endoabs.65.P424

P425

Severe proximal myopathy with high creatine kinase levels secondary to Hashimoto's thyroiditis

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A 30-year-old teacher with no past medical history presented with a 3 month history of muscle weakness, pain and spasms together with cold intolerance, weight gain and fatigue. She had a baby 4 months prior to this and 2 months after delivery noticed palpitations, insomnia and tiredness which resolved spontaneously. She was a non-smoker who did not consume alcohol. She was not on any medication. There was no family history of endocrinopathy. Clinical examination revealed proximal muscle weakness with tenderness and a small non-tender goitre. There were no other positive findings. Her Creatine Kinase (CK) was elevated at 5124 U/l. Hypothyroidism was suspected but due to her clinical presentation and a raised CK; myopathy was investigated. This included a Viral screen, Cortisol, Prolactin, Vitamin B12 and D, ESR, rheumatoid factor, auto-antibody screen; all of which were normal. Primary Hypothyroidism due to Hashimoto's Thyroiditis was confirmed with a TSH 190 mU/l, Free T4 < 5 pmol/l and Free T3 2.7 pmol/l. Thyroid Peroxidase Antibodies >1000/U/ml. Cause for myopathy was unclear apart from Primary Hypothyroidism so she was treated with Levothyroxine which led to normalization of CK and resolution of myopathy over 4 months.

Discussion

Myofibre degeneration and decreased rate of clearance of CK from circulation has been suggested as a cause of raised CK in Hypothyroidism. Statin induced hypothyroid myopathy and myopathy due to relative hypothyroidism resulting from rapid thyroid hormone reduction in a hyperthyroid patient have been reported. This case is noteworthy in that without an apparent precipitant there was simultaneous onset of symptoms suggestive of hypothyroidism and myopathy with complete resolution of symptoms and normalization of CK with thyroxine replacement.

Conclusion

Expect recovery of myopathy to lag behind by 3–6 months after normalization of TSH. Thyroid function should be routinely checked in cases presenting with either myopathy or raised creatine kinase. Full case report previously published in *BMJ Case Rep* 2019, DOI: 10.1136/bcr-2019-230427.

DOI: 10.1530/endoabs.65.P425

P426

A reversible cause of pulmonary hypertension

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Graves' disease is one of the reversible causes of pulmonary hypertension (PAH). The association was first reported in 1980. Studies have suggested an elevated pulmonary artery systolic pressure in about 36% of patients with Graves' disease by Doppler echocardiography. We report a case of Graves disease associated with pulmonary hypertension in a young female.

Case report

A 41 year old female presented with history of worsening breathless and palpitations. She had atrial fibrillation with fast ventricular rate and a large right side pleural effusion. Her Thyroid functions showed FT4 of >100 (10.8–25.5 pmol/l), FT3 40.2 (3.1–6.3 pmol/l) and TSH <0.03 (0.27–4.20 mU/l). She had positive thyroid peroxidise antibodies (TPO) 450 (0–109 IU/ml) and positive TSH receptor antibodies (TRAB) 17.4 (0–1.5 U/l). She was treated with carbimazole, propranolol and prednisolone. She was readmitted a month later with thyrotoxic storm, heart failure, right side pleural effusion and pulmonary odema. CT thorax showed an enlarged main pulmonary artery and an Echocardiogram showed estimated pulmonary artery pressure high at 43–48 mmHg. She received radioiodine and remains on low dose of carbimazole. Her recent thyroid functions are FT4 of 17.9, FT3 6.4 and TSH 0.15. Her Echocardiogram 4 months after the treatment showed an estimated pulmonary pressure of 25 mmHg.

Discussion

Pulmonary arterial hypertension (PAH) is defined as a mean pulmonary artery pressure (mPAP) of >25 mmHg at rest or >30 mmHg after exercise. In hyperthyroidism, increase in cardiac output and an elevated peripheral vascular resistance (PVR) result in elevation of pulmonary artery systolic pressure. TRAb also has a link with PAH suggesting an autoimmune etiology. Echocardiography may underestimate pulmonary artery systolic pressure in patients with severe pulmonary hypertension. In summary, hyperthyroidism is a cause of reversible pulmonary hypertension. Most of the patients have mild and asymptomatic pulmonary hypertension but exacerbation of PAH occurs in a fraction of these patients and may be the only manifestation. The prognosis in such cases depends solely on early detection and successful treatment of hyperthyroidism.

DOI: 10.1530/endoabs.65.P426

P427

Managing hypothyroidism without oral levothyroxine

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Introduction

Hypothyroid patients with failure to take/absorb oral levothyroxine might require intravenous levothyroxine. IV levothyroxine is neither licensed nor available in UK. It has to be imported (with special request), and is unexpectedly costly. IV liothyronine has shorter duration of action, need 2–3 injections/day, and exhibits sudden surges increasing risk of angina/arrhythmia. Moreover, IV liothyronine is much more expensive than IV levothyroxine.

Case report

50 year old lady presented to endocrine OPD with sub-optimal TFTs. She is hypothyroid since 2008 (previously well controlled). She has been suffering from intractable vomiting and abdominal pain since 2012. Diagnosed to have gastroparesis (2013) and slow colonic transit with obstructive defecation (2014). Though initially responded well to gastric pacemaker (2014), it was removed due to persistent pain, with resultant deterioration of vomiting after any oral

intake. Developed metoclopramide induced hyperprolactinemia/galactorrhoea (2014), which subsided on withdrawal. Diagnosed to have myenteric ganglionitis with malabsorption and was put on long term total parenteral nutrition (2014), after a failed feeding jejunostomy trial. On 11 March 2019, TSH was 13 mU/l (0.2–4.5) and FT4 was 10.4 pmol/l (11–23). She was on 400 mcg of levothyroxine (20 ml solution spread out during the day in 2 ml sips), colecalciferol 20 000 units (alternate days), and vitamin B12 (injection). In view of sub-optimal TFTs, intravenous levothyroxine was started as 100 mcg once weekly in 100 ml 0.9% sodium chloride over 30 min (day unit, cardiac monitoring with TFT prior to each dosing). IV levothyroxine was increased in 100 mcg increments to 200 mcg twice weekly. Oral levothyroxine suspension weaned off in few weeks. IV liothyronine was not considered due to reasons described (introduction). On 8 April 2019, TSH was 4.5 mU/l and FT4 12 pmol/l. Found to have osteoporosis which was treated with annual intravenous zolendronic acid injections.
Conclusion
This case highlights the various hurdles involved in the treatment of hypothyroid patients with malabsorption.

DOI: 10.1530/endoabs.65.P427

P428

Myxoedema coma with severe hypoxia

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Myxoedema coma is a rare Endocrine emergency.
Case report
28 year old Polish woman, recently travelled to the UK, presented to the A&E with 3 week history of breathlessness and bilateral leg swelling. She had a history of Trisomy 21, was not taking any medications. She had amenorrhoea for 4 months and orthopnoea with periorbital oedema with conjunctival congestion. Saturation 70% on air, 96% on 15 l of oxygen, heart rate 42, blood pressure 103/61, temperature 36.2. Echocardiogram showed 3.3 cm pericardial effusion and tests showed TSH >100 mIU/l (0.4–4.4) with FT4 0.05 pmol/l (12–22). She initially had type 1 respiratory failure and required intubation and ventilation. Pericardial effusion was drained twice. She was treated with intravenous liothyronine and hydrocortisone along with levothyroxine via nasogastric tube. A CT pulmonary angiogram showed bilateral lower zone collapse and complete collapse of the left upper lobe with widespread ground-glass consolidation throughout the remaining aerated lung with an element of congestive failure. Despite pericardial drainage, she later developed type 2 respiratory failure and despite intubation and ventilation required transfer for surgical tracheostomy and long wean from ventilation. She was discharged on oral levothyroxine and nocturnal CPAP.
Discussion
Our patient had large pericardial effusion and respiratory failure, both rare complications of severe myxoedema. Pericardial effusion is described in literature as a complication of myxoedema. These usually are exudative with high cholesterol content, but can occasionally be transudative. Respiratory failure is well recognised in myxoedema with reduced ventilatory response to carbon dioxide, decreased diffusion capacity, respiratory muscle weakness and decreased breathing capacity. Abnormalities suggestive of fibrotic lung disease have been described. Ventilatory response usually improves after treatment. In our patient, this did not happen and it took over two months to wean her off. Ground glass consolidation and hypoxia requiring prolonged ventilation and tracheostomy is very rare.

DOI: 10.1530/endoabs.65.P428

P429

Audit of the use of TRAb testing first-line in the evaluation of hyperthyroidism

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Graves' disease (GD) is the most common cause of hyperthyroidism[1] and is caused by stimulating autoantibodies to the TSH receptor (TRAb).[2] TRAb assays have 98% sensitivity and 99% specificity [3] for GD and are recommended as the first-line cost-effective investigation to diagnosis the aetiology of hyperthyroidism and determine the risk of thyroid eye disease.[4,5] In TRAb antibody negative patients, radionuclide imaging may be helpful in demonstrating focal increased uptake (toxic nodular disease) or absent uptake (thyroiditis). We audited our diagnostic work-up of new cases of hyperthyroidism presenting to King's College Hospital, London between 1 January 2018 to 30 June 2018. We identified 56 patients (48 female and 8 male); age range 20–92 years. TRAbs were measured in $n=44$ patients: TRAbs were elevated in $n=21$, measurable but within the reference range in $n=8$, and undetectable in $n=15$. Of the $n=15$ TRAb negative patients; $n=6$ had convincing clinical/biochemical evidence of a thyroiditis; $n=3$ demonstrated spontaneous remission of thyrotoxicosis and $n=2$ underwent technetium uptake scans which showed features typical of GD. $N=4$ patients did not attend requested imaging investigations. Of the $n=8$ patients with measurable but normal range TRAbs, $n=2$ were managed as GD, $n=3$ underwent technetium uptake scans which showed features typical of GD, $n=2$ had clinical/biochemical features suggestive of a thyroiditis and $n=1$ demonstrated resolution of thyrotoxicosis. $N=2$ patients underwent nuclear medicine imaging as a first-line diagnostic investigation to establish the aetiology of hyperthyroidism; $n=1$ revealed an autonomously functioning nodule and $n=1$ nodules with no focal autonomy. $N=10$ patients had neither TRAb nor nuclear medicine imaging as first line investigation; of these $n=5$ had evolving/sub-clinical disease, $n=5$ were observed. In conclusion, TRAb testing was performed first-line in 79% of new referrals for hyperthyroidism. We are working towards clinicians adopting a more consistent approach to determining the aetiology of hyperthyroidism.

DOI: 10.1530/endoabs.65.P429

P430

Iododerma following radioiodine treatment for Graves' thyrotoxicosis

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Introduction
Iododerma is a hypersensitive skin reaction that occurs after exposure to Iodine. It is a well-known adverse reaction after intravenous iodine-containing contrast medium, but cases occurring after oral exposure are rare. A six-year follow-up study in one centre looking for any skin lesions occurring after oral radioiodine therapy for thyrotoxicosis, noted an incidence rate of 2.1% in 141 patients. The skin lesions can be acneiform, erythematous, urticarial, hemorrhagic, vesiculo-bullous, pustular, carbuncular, petechial, or nodular. Lesions generally appear 4–6 weeks after exposure and disappear within 6 months. We present an interesting case.
Case
A 57-year-old lady presented with several painless lumps and an erythematous rash affecting the skin of both legs. The patient was otherwise well. Within two weeks prior to this, the patient had been given an oral dose of radioiodine (I-131) for the treatment of chronic thyrotoxicosis. The patient had a past medical history of Graves' thyroid eye disease and coeliac disease. There was no past history of iodine allergy. The patient had not started any other medication prior to this presentation. Because the patient was still radioactive after a recent dose of I-131 therapy the patient could not be physically examined at presentation. However, the patient sent in a picture, which demonstrated these lesions. A diagnosis of erythematous and nodular iododerma was discussed and the patient was reassured that the lesions are usually self-limiting. A repeat assessment 3 months later demonstrated that the nodules were resolving but the skin discoloration was still present.
Conclusion
The diagnosis of iododerma is mostly clinical, based on the history and physical examination. Our patient had cutaneous manifestations soon after receiving I-131 therapy. Patients need to be made aware of this rare, self-limiting side-effect when consenting for radioiodine therapy for the treatment of thyrotoxicosis.

DOI: 10.1530/endoabs.65.P430

P431

Macro TSH in a case of 'poorly controlled' hypothyroidism

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A 41-year old lady with hypothyroidism for 20 years attended the endocrinology clinic for persistently raised TSH levels despite high dose levothyroxine. Past

medical problems – depression, psoriasis, obesity, cholecystectomy. Her hypothyroidism was well-controlled until 2016 but since then, her TSH concentration had risen significantly to >100 mU/l with normal free T4. Levothyroxine had been increased in steps to 200 mcg/day. Despite the increased dose, the TSH concentration varied between 8.4 and 11.7 mU/l with normal free T4 levels. Clinically, she did not have significant symptoms of hypothyroidism, examination was unremarkable apart from her weight of 109 kg. She denied poor compliance with her medication. Her medications did not include any drugs which interact significantly with levothyroxine. Investigations including B12, folate, iron studies, calcium, transglutaminase antibodies, HbA1C – unremarkable. Short Synacthen test normal. TSH measurements repeated on different platforms but were still high. Macro-TSH assay – approximately 80% of the total TSH.

Conclusion

It is not unusual to see patients who have normal free T4 levels with raised TSH level in the context of subclinical hypothyroidism. There are many causes of persistent TSH elevation in patients on thyroxine replacement. These include poor compliance with treatment, drugs that interfere with absorption and other causes of malabsorption. Assay interference including macro-TSH should be considered in the differential diagnosis. Macro-TSH is a large TSH molecule which is formed between anti-TSH antibody and TSH which has low bioactivity. It can cause falsely elevated TSH.

DOI: 10.1530/endoabs.65.P431

P432

Value of thyroid fine needle aspiration and cytology in clinical practice

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Introduction

Thyroid nodules have a prevalence of 50% in the adult population in the UK. The risk of cancer is significantly lower if the nodules are a part of multi-nodular goitre. Fine needle aspiration and cytology (FNAC) is an important tool to assess the risk of malignancy in thyroid nodules.

Method

We audited the safety and efficacy of management of thyroid nodules at Bolton in accordance with British Thyroid Association and Royal College of Pathologists guidelines. Data of 30 consecutive patients were collected from their case notes, radiology results and lab results and then analysed. All data expressed as Mean (s.d.).

Results

The mean age of the patients was 53.4 (17.5) years. 83.3% were females. Thyroid function tests were checked in all patients. 83% of initial FNACs were performed by ENT surgeons without US guidance and 17% performed by Radiologists were with US guidance. Out of the initial FNACs, Thy1-46%, Thy1c-17%, Thy2-27%, Thy2c-0, Thy3-7% and pus aspirated from a nodule in 1 case (3%). FNAC was repeated by Radiologists in 4 and ENT surgeons in 13 cases with similar US support. The results after the second FNAC were Thy1-47%, Thy1c-12% and Thy2-41%. 14 (47%) cases were discharged after 1st or 2nd FNAC results. Among the rest, 1 was too ill for surgical intervention and 2 went to the independent sector for their surgery. Amongst the rest, 2 underwent total thyroidectomy and one of them had Hurthle cell cancer. Out of the 11 who underwent hemithyroidectomy, one was found to have papillary thyroid carcinoma.

Conclusions

The overall pickup rate of cancer was 7.4% of all patients who had undergone FNACs in our cohort of patients audited. We may be able to refine our diagnosis and reduce surgery if all 2nd FNACs were performed under US guidance.

DOI: 10.1530/endoabs.65.P432

P433

Discordant thyroid function tests due to immunoassay interferance – case report

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77 year old gentleman was referred to endocrine clinic at Manchester Royal Infirmary in June 2017 due thyrotoxicosis with TSH 0.10 mu/l, free T4 24.3 pmol/l, and free T3 15.7 pmol/l. He was presented at that time with symptoms of tiredness, fatigue and tremor. He was initially treated with antithyroid drugs from June 2018 till May 2018 with radioactive iodine 579 MBq in May 2018. Subsequently, he developed symptoms of excessive tiredness, lack of energy, weight gain and cold intolerance which raised the possibility of post radioiodine hypothyroidism. His thyroid function test in August 2018 showed TSH 5.8 mu/l, free T4 8.0 pmol/l and free T3 9.9 pmol/l and he was commenced on levothyroxine 50 mcg daily. His repeated thyroid function in November 2018 revealed TSH 3.5 mu/l, and free T4>100.0 pmol/l. However, clinically he remained hypothyroid with symptoms of weight gain, fatigue and cold intolerance. Levothyroxine has been stopped temporarily and his repeated thyroid function test in January 2019 showed TSH 5.9 mu/l, free T4 38.8 and free T3 8.5. There was a clear discrepancy between clinical status and thyroid function test. Moreover, there was an evident of discordant (paradoxical free T4 and TSH levels) suggesting acquired assay interference. Therefore, a sample was sent to Salford Royal Hospital and the result was:

Sample	Manchester Royal Hospital	Salford Royal Hospital
TSH (mu/l)	5.9	98
Free T4 (pmol/l)	38.8	<1.3
Free T3 (pmol/l)	8.5	–

The results from Salford Royal Hospital seem correlate clinically and suggest that there has been Roche assay interference. He was recommenced on levothyroxine treatment in January 2019 and the dose has been optimized to 125 mcg daily with good clinical response and normalisation of TSH. Immunoassay interference is a well described phenomenon. Clinicians need to be aware of the potential for assay interference since it may lead to inappropriate treatment. Normal reference range: TSH (0.2–5.0 mu/l), Free T4 (9–24 pmol/l), Free T3 (3.6–6.4 pmol/l).

DOI: 10.1530/endoabs.65.P433

P434

Concomitant Graves' & (?) ectopic parathyroid adenoma

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This case illustrates a decision paradox on investigations (to exclude secondary hypercalcaemia) and treatment options (in unresponsive thyrotoxicosis despite supra-normal doses of carbimazole). A 56-year-old lady, who was referred with hyperthyroid symptoms and evidence of biochemical thyrotoxicosis, was also found to have symptomatic hypercalcaemia (constipation & polyuria). Investigations were as follows: FT4 >100 pmol/l, TSH <0.02 mU/l, TRAb positive, Ca 3.0 mmol/l, PTH 2 pmol/l, Vitamin D <34 nmol/l & urine calcium 17.6 mmol/24 h. Thyroid ultrasound and sestamibi were suggestive of Graves' disease (GD) and in addition, a mediastinal parathyroid adenoma was identified adjacent to the aortic arch. Parathyroid adenoma was suspected because of severe hypercalcaemia with symptoms, inappropriately normal PTH, Increased 24 h urinary calcium excretion & suggestive sestamibi scans. Since the patient had uncontrolled thyrotoxicosis despite 120 mg carbimazole per day, she was urgently referred for thyroidectomy and parathyroidectomy to a tertiary centre, after adequate beta-blockade. After resection of both, the histology report from the mediastinal lesion was indicative of ectopic thyroid tissue. We are arranging for immunocytochemistry, as reports of parathyroid tissue mimicking thyroid tissue are recognized in the literature. Radiological features can be ambiguous when the early differential washout of sestamibi tracer from the thyroid could be lost because of GD. This raises a question of specificity for subtraction Tc-99m sestamibi and iodine-123 scintigraphy in patients suspected to have coexistent GD and primary hyperparathyroidism.

Unanswered questions

1) How confirmatory is histopathology report to confirm ectopic thyroid without immunocytochemistry?
2) Biochemistry suggests primary hyperparathyroidism.
3) Would a 2-step approach of initial thyroid surgery negate the need for mediastinal exploration?

4) Should we have done a subtraction Tc-99m sestertii and iodine-123 scintigraphy?
5) Should we have considered Lithium therapy in carbimazole unresponsive thyrotoxicosis?

DOI: 10.1530/endoabs.65.P434

P435

Early diagnosis and prompt treatment of severe thyrotoxicosis in patients with congestive cardiac failure is critical: lessons from a case of type 1 amiodarone induced severe thyrotoxicosis

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Cardiac failure is a rare manifestation of thyrotoxicosis in patients without heart disease. However, patients with prior cardiac failure are at high risk of decompensation with thyrotoxicosis. Amiodarone is a widely used antiarrhythmic agent and amiodarone induced thyrotoxicosis (AIT) is not an uncommon complication. We present a case. A 48-year old male with intermittent atrial flutter, dilated cardiomyopathy, myocardial infarction and stroke was referred for severe thyrotoxicosis. He had been taking amiodarone for three years and developed thyrotoxic symptoms four weeks ago. Her mother had thyrotoxicosis. Examination confirmed signs of thyrotoxicosis and a subtle diffuse goitre. Investigations showed fT4 of more than 100 pmol/l, fT3 of 36.4 pmol/l, suppressed TSH and normal ESR. He was started on high dose Carbimazole. Beta blocker was commenced and amiodarone stopped in liaison with cardiologist. Thyroid peroxidase and thyroid receptor antibodies were later found to be positive and patient declined thyroid imaging. He became clinically and biochemically euthyroid on titration regimen of carbimazole but beta blockers were continued for underlying cardiac failure. He is currently awaiting thyroidectomy. Amiodarone can cause thyrotoxicosis by two distinct mechanisms. AIT type 1 is caused by iodine toxicity from amiodarone and is treated with anti-thyroid drugs. AIT type 2 is due to thyroiditis causing release of thyroid hormones and is treated with steroids. This case had many features suggestive of AIT type 1 but, if in doubt, such patients should initially be treated with both anti-thyroid drugs and steroids and response monitored. Early recognition and prompt treatment is important to avoid worsening of pre-existing cardiac failure or ischaemic heart disease due to high cardiac output state. Close liaison with cardiologist to stop amiodarone and to optimise medical management of cardiac failure is essential but amiodarone discontinuation alone may not control thyrotoxicosis due to its long half-life.

DOI: 10.1530/endoabs.65.P435

P436

Amiodarone induced thyroiditis in congenital heart disease – how long should we continue steroids?

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A 38-year male with background history of Tetralogy of Fallot which had been surgically corrected, presented with symptomatic supraventricular tachycardia in July 2015. This required amiodarone therapy. Thyroid function was normal prior to starting amiodarone. Amiodarone therapy was discontinued in July 2017 when he converted to sinus rhythm. Seven months after stopping treatment, he presented to A&E with signs and symptoms of hyperthyroidism. His TSH was < 0.03 mU/l (0.27–4.2), T4 154 pmol/l (12–22) with negative thyroid antibodies. The Burch–Wartofsky score was 35, suggesting an impending thyroid storm. An ultrasound showed thyroiditis with no increased vascularity. He was treated with propylthiouracil 200 mg tds, which was increased thereafter to 300 mg tds and prednisolone 30 mg as well as Lugols iodine. After 6 weeks of this treatment his T4 reduced to 61 pmol/l with TSH of <0.03 mU/l. Prednisolone was discontinued at this stage and within 10 days the T4 was again >154 pmol/l with a TSH<0.03 mU/l. A Tc uptake scan was performed which showed no uptake. Prednisolone 60 mg was commenced and propylthiouracil was increased to 300 mg 6 times daily and continued for 3 months with a dose reduction over time. By the end of July 2018 his thyroid function had come under control (ft4 9.8 pmol/l, TSH 15.3 mU/l). He underwent thyroidectomy in October 2018. There are two types of amiodarone induced thyroiditis. In this case we opted to treat for both simultaneously. This gentleman required a long admission and frequent close discussion with a tertiary centre. At one stage an urgent thyroidectomy was felt to be required, however he eventually began to respond to the combination of longer term steroid treatment and PTU. This case highlights that it is unpredictable how long steroids will be required and close follow up of response is needed to judge when to stop.

DOI: 10.1530/endoabs.65.P436

P437

Radioactive iodine therapy dose for recurrent thyrotoxicosis

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Aim

To determine the current practice of radioiodine dose treatment provided in Hull and East Yorkshire NHS Trust, in line with the recommended guidelines of the Royal College of Physicians and published data.

Methods

The medical records of the patients who received more than one dose of radioactive iodine for the treatment of thyrotoxicosis in Hull and East Yorkshire NHS Trust between 2006 and 2018 were reviewed retrospectively. The level of the biochemical thyroid function tests including thyroid stimulating hormone, free T4 and free T3 was recorded. The number of how many doses of radioactive iodine treatment was calculated. Each dose of radioactive iodine therapy was noted.

Results

The average range of age in our study is between 28 and 82 with average age at 54.5. The percentage of female gender was 73% while male sex was 28%. During the study period, a total of 33 patients received more than one dose of radioactive iodine. 60% had diagnosis of Grave's disease, 37% had multinodular goitre and 3% had toxic adenoma. Analysis of biochemical average thyroid function test showed 36.5% had T4, T3 from 1 to 1.5 times above normal level, 54.5% had T4 and T3 from 1.5 to 2 times above normal range and 9% had from 2 to 3 times T4, T3 above normal range. Looking at initial medical treatment, 88% received carbimazole and 12% had propylthiouracil as they were intolerant to carbimazole. The dose of antithyroid medication was variable according to thyroid function test. 100% of patients received a radioactive iodine dose of 400 MBq either in the as a first dose of radioactive iodine or in subsequent doses. 9% of the patients received three times of radioactive iodine treatment and 91% received two times radioactive iodine treatment with optimal responses.

DOI: 10.1530/endoabs.65.P437

P438

A rare complication of thyrotoxicosis: diabetic ketoacidosis

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Graves' disease is a common autoimmune disease causing hyperthyroidism. Thyroid has a catabolic effect on carbohydrate metabolism especially in the hyperthyroid state. We describe a rare complication of thyrotoxicosis in a patient with type II diabetes on insulin, with no previous thyroid history. An 83 year old woman with type 2 diabetes on biphasic insulin presented with symptoms of polyuria, polydipsia and fatigue. She was tachycardic and tachypneic but normotensive and apyrexial with no obvious focus of infection. Her clinical examination revealed no abnormalities and initial investigations showed blood glucose of 26 mmol/l, ketones 4.8 mmol/l, pH 7.19 and bicarbonate of 14 confirming diagnosis of Diabetic Keto-Acidosis (DKA). A thyroid function panel was ordered which showed her thyroid stimulating hormone was <0.003 with a free T4 level of 64.1 ug/l. She was also positive for thyroid stimulating hormone receptor antibody (TSH-R), confirming Graves' disease. Our patient improved upon starting management for DKA with resultant closure of anion gap and

resolution of DKA. Treatment for thyrotoxicosis was also initiated with propranolol and carbimazole to manage her thyroid state with good response. She was discharged once medically recovered back on biphasic insulin and newly commenced on anti-thyroid medication. Our case emphasizes the impact of thyroid state on diabetes control and the potential complications of uncontrolled hyperthyroidism in patients with diabetes. Increased glucose uptake and increased insulin clearance in hyperthyroidism creates a relative insulinopenic state that can manifest as DKA. Graves' thyroid patients with diabetes can have suboptimal blood sugar control in hyperthyroid state and they should be warned about DKA as a potential complication.

DOI: 10.1530/endoabs.65.P438

P439

Large Pericardial Effusion due to Primary Hypothyroidism

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A 54 years old gentleman was admitted to cardiology ward from echocardiography department in view of findings on the scan. He was referred to cardiology clinic on outpatient basis 3 months earlier by his GP for his shortness of breath, ankle swelling and a murmur heard on auscultation by his GP. His transthoracic echocardiography was being conducted prior to attendance at cardiology clinic. The result showed a large global pericardial effusion, max 4.9 cm in size. There was severe aortic regurgitation as well. He underwent thyroid function test as part of screening to find out cause for pericardial effusion and his TSH was 186 mU/l along with T4 of 5.4 pmol/l. His anti-TPO was elevated at 289 U/ml. At this point an endocrinology opinion was sought. On further questioning the patient mentioned that he was feeling tired, lethargic, cold and constipated for the last 3 months, along with noticing the shortness of breath and swelling to his ankles. He also noticed that his skin was feeling dry and had noticed some hair loss. He was also feeling low in mood. There was no past medical history of note. On examination he had facial plethora and loss of eyelashes. He also had slow relaxing ankle reflexes. A diagnosis of primary hypothyroidism was made. Subsequently he was started on low dose levothyroxine and the dose was gradually titrated up. A discussion was held in cardiology MDT meeting and it was decided to manage his pericardial effusion conservatively. He stayed in hospital for 10 days and started to feel better after initiation of levothyroxine. This case illustrates that hypothyroidism should be considered in the differential diagnosis of patients presenting with unexplained pericardial effusion.

DOI: 10.1530/endoabs.65.P439

P440

Thyroiditis in a returning traveller

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Thyroiditis can often lead to initial thyrotoxicosis and it is important to differentiate among the causes as many cases do not require antithyroid drugs. We present a case report of a 48 year old lady who presented with 10 days history of fever, fatigue, myalgia and a painful goitre after returning from a cruise at Caribbean. Examinations showed pyrexia of 38 C but no localising signs of infection. She had a smooth tender goitre and no signs of thyrotoxicosis. Investigations revealed modestly raised white cell count and C-reactive protein and deranged liver function tests with significant ALT rise. Thyroid function tests showed TSH of 0.07 mIU/l (0.25–5.00), fT4 of 29.2 pmol/l (9.0–23.0) and fT3 of 7.3 pmol/l (3.5–6.5). Interestingly, thyroid function tests were completely normal seven days ago. Thyroid auto-antibodies were negative and thyroid uptake scan showed no thyroid tracer activity. Two months later, her symptoms had disappeared. There was no palpable goitre and thyroid function tests showed normal fT4, normal fT3 and a slightly high TSH suggesting subclinical hypothyroidism. Inflammatory markers and liver function test had normalised. She was diagnosed to have de Quervain's thyroiditis and was monitored without antithyroid drugs. De Quervain thyroiditis is thought to be due to a viral illness and the management is conservative. Treatment with antithyroid drugs is not indicated as the initial thyrotoxicosis is linked to cytotoxic T-cell mediated release of thyroid hormones into blood stream rather than increased thyroid hormone production. A close watch should be kept on thyroid function tests as patients go through a hypothyroid phase due to depletion of thyroid hormones before returning to euthyroid phase in most cases.

DOI: 10.1530/endoabs.65.P440

P441

Inhibitory actions of diketopiperazines within the thyroid gland, and their system-wide presence

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C-terminal derivatives of hormones commonly have secondary actions. This is a well-established phenomenon, seen in the case of oxytocin, parathyroid hormone and alpha-melanotropin. Such derivatives can either complement or antagonise the action of the parent hormone. Thyroid-releasing-hormone (TRH) undergoes cleavage and cyclisation to form the C-terminal derivative histidinyl-proline-diketopiperazine (His-Pro-DKP). Despite conventional function via the endocrine HPT axis, the local presence of TRH within the thyroid gland led to the investigation of TRH function upon thyroid follicular cells in culture, where it was found to have an inhibitory effect upon thyroglobulin (Tg) secretion. This is retained via the C-terminal His-Pro-DKP, and suggests a potential downstream inhibition upon thyroid hormone production. Such results imply bifunctional activities of hormones via actions of their secondary derivatives, where TRH conventionally acts to increase Tg secretion. The presence of TRH-like peptides, which differ to TRH due to a substitution of the histidine amino acid, encouraged the exploration of DKP formation from these peptides also. In addition to their presence within the thyroid, these peptides are present within organs such as the prostate and the testes. It was found that these also undergo intramolecular cyclisation to form such C-terminal derivatives, with structures specific to the parent peptide. Such cyclisation was increased in the presence of phosphate ion and is proposed to occur due to the function of a dipeptide cyclase. Hence, subsequent investigations were undertaken to study the effect of these DKPs on hormone activities in prostate and Leydig cell lines. Such functions may indicate an effect of DKPs upon regulation of cellular secretions in a system-wide manner, in addition to the conventional actions of the parent hormone.

DOI: 10.1530/endoabs.65.P441

P442

Multiple Mieloma associated with Graves disease – case presentation

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Although it is well known that aplastic anemia and agranulocytosis are potential lethal adverse reactions of antithyroid treatment, we present a case of methimazole administration in a patient with bone marrow transplant for multiple myeloma, with favorable evolution. We present the case of a 43 y.o. male, known with Grave's disease since 2010 (on ATS treatment for only 6 months), vitiligo, systemic sclerosis and type 1 diabetes, diagnosed with multiple mieloma Ig G Tipe, Stage III C in 2017. He received treatment with Velcade – Dexametazone chemotherapy and auto transplant. Pancytopenia, hyperproteinemia, severe inflammatory sindrome and tumoral lysis syndrome were noticed in the evolution of the hematological disease, though, with good clinical and paraclinical recovery process. He presented recently in our clinic with a very suggestive clinical profile of hyperthyroidism recurrence. Blood tests confirmed high level of thyroid hormones: TSH= 0.005 mU/l, fT4= 28.9 pmol/l (10.4–19.4), fT3= 7.9 pmol/l (2.4–6.8), TRAb= 4.7 U/l and normal full blood count. Despite the previous bone marrow suppression, in the absence of the possibility of radioiodine therapy, Methimazole treatment was started in a dosage of 10 mg per day with careful FBC monitoring. The evolution on low ATS dose was favorable and without adverse reactions till present. The transplant immunosuppression protocol can have

favorable effect on the evolution of autoimmune diseases. In this case, a low ATS dose was sufficient to normalize the thyroid function. The association of multiple myeloma with autoimmune diseases is frequent, but the pathogenesis still remains unknown. Thyroid function must be performed periodically. ATS treatment should be administered only after taking into consideration the possible presence of pancytopenia.

DOI: 10.1530/endoabs.65.P442

P443

The need to update patient safety information on carbimazole

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Hyperthyroidism commonly affects women of child-bearing age. Use of carbimazole in the first trimester of pregnancy has been shown to be associated with certain congenital abnormalities, such as aplasia cutis, choanal atresia, dysmorphic facial features, abdominal wall and gastrointestinal tract defects, in up to 2% of cases. The MHRA issued a Drug Safety Alert in February 2019, recommending to strengthen the advice on contraception given to women of child-bearing age who need treatment with carbimazole, particularly at a dose above 15 mg a day. In the Endocrinology Department at Frimley Park Hospital, we have adapted our practice with the aim that contraception and plans for pregnancy will be discussed with all female patients of child-bearing age. We addition, we reviewed the Trust patient information leaflet on anti-thyroid medication, which had previously not mentioned the use of carbimazole in pregnancy. We studied the available literature on the topic and added a section to our leaflet discussing the risks of congenital malformations linked to carbimazole. We have included advice on using effective contraception while taking the medication and recommendations to discuss switching to propylthiouracil in the event of pregnancy or if planning a pregnancy, as this is considered safer in the first trimester. We aim to reduce the risk of teratogenic effects of carbimazole in the first trimester of pregnancy by ensuring our patients are better informed about the medication, the need for effective contraception and when to seek advice regarding their management.

DOI: 10.1530/endoabs.65.P443

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