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Plenary Lectures

Society for Endocrinology International Medal Lecture

PL1

Primary hyperparathyroidism: molecular genetic insights and clinical implications

Andrew Arnold
University of Connecticut School of Medicine, Farmington, Connecticut, USA.

Primary hyperparathyroidism, a common endocrine disorder manifested by hypercalcemia and excessive parathyroid hormone levels, is most often due to a benign parathyroid adenoma but can also result from multigland involvement or, rarely, from malignant parathyroid neoplasia. Further, while most cases of primary hyperparathyroidism have a nonfamilial/sporadic presentation, an important minority occurs in the setting of strong familial predispositions. In recent years much has been learned about the heritable genetic mutations responsible for, or contributing to, the major familial hyperparathyroid syndromes, including multiple endocrine neoplasia types 1 and 2A, the hyperparathyroidism-jaw tumor syndrome (HPT-JT), familial hypocalciuric hypercalcemia, neonatal severe hyperparathyroidism, and familial isolated hyperparathyroidism; important insights into the acquired driver mutations underlying sporadic parathyroid tumors have also accrued. The direct role of the oncogene cyclin D1 in human neoplasia was first established in parathyroid adenomas, followed by recognition of its importance in other tumors such as breast and squamous cell cancers, mantle cell lymphoma, and multiple myeloma. Recent insights into the landscape of somatic driver mutations in parathyroid carcinoma, including the discovery of recurrent alterations in the PI3K/MTOR pathway, carry immediate therapeutic implications in the setting of metastatic disease where effective treatment has been lacking. Recognition of predisposing germline mutations can have significant implications in patient management, for example in preventing parathyroid carcinoma in HPT-JT, and in optimizing the approach to parathyroidectomy in MEN1. Finally, the existence of lower penetrance germline variants in common sporadic hyperparathyroidism is an emerging area of interest.

DOI: 10.1530/endoabs.50.PL1

Clinical Endocrinology Trust Lecture

PL2

Mechanisms underpinning human insulin resistance

David Savage
University of Cambridge, Cambridge, UK.

Adipose inflammation is increasingly percieved to be a major factor in the pathogenesis of obesity associated insulin resistance. However, human evidence supporting this hypothesis remains largely unconvincing. An alternative model is suggested by observations made in patients with rare forms of lipodystrophy; namely that a relative inability to cope with sustained surplus energy intake underpins insulin resistaance. Recent data suggesting that subtle forms of lipodystrophy are much more prevalent than previously appreciated will be presented and discussed.

DOI: 10.1530/endoabs.50.PL2

Society for Endocrinology Transatlantic Medal Lecture

PL3

What to watch: three breakthroughs that may change our lives in the next 10 years

Teresa Woodruff
Northwestern University, Chicago, Illinois, USA.

Facing a cancer diagnosis at any age is devastating. However, young cancer patients have the added burden that life-preserving cancer treatments, including surgery, chemotherapy, and radiotherapy, may compromise their future fertility. The possibility of reproductive dysfunction as a consequence of cancer treatment has a negative impact on the quality of life of cancer survivors. The field of oncofertility, which merges the clinical specialties of oncology and reproductive endocrinology, was developed to explore and expand fertility preservation options and to better manage the reproductive status of cancer patients. Fertility preservation for females has proved to be a particular challenge because mature female gametes are rare and difficult to acquire, but combined with cutting edge techniques and government policies, the next 10 years could hold more promise for reproductive science.

DOI: 10.1530/endoabs.50.PL3

Society for Endocrinology Starling Medal Lecture

PL4

Next generation tools to understand endocrine function in health and disease

David Hodson
University of Birmingham, Edgbaston, UK.

Type 2 diabetes (T2D) currently affects ~10% of the UK adult population and is one of the foremost health challenges currently facing society. This syndrome can be described as a failure of the pancreatic beta cell mass to secrete sufficient insulin to counteract elevated blood glucose levels. It is largely believed that all beta cells are the same. However, recent studies have shown that beta cells in fact comprise discrete subpopulations, some of which may contribute to insulin secretion and T2D more than others. This presentation will highlight the methodology that has allowed us to redefine how beta cells- and more generally endocrine cells- function. The influence of subtle differences in the beta cell 'barcode' on insulin release in health and disease will then be examined. Finally, new techniques, which may provide unprecedented insight into T2D and drug development, will be discussed.

DOI: 10.1530/endoabs.50.PL4

Society for Endocrinology Dale Medal Lecture

PL5

Abstract unavailable.

Society for Endocrinology European Medal Lecture

PL6

Corticosteroids and the brain

Marian Joels
University Medical Center Utrecht, Utrecht, The Netherlands.

Corticosteroid hormones are synthetized in the adrenal glands and reach many organs including the brain. Within the brain they exert their actions through mineralocorticoid (MR) and glucocorticoid receptors (GR). These receptors generally act as transcriptional regulators and change the function of brain cells in a slow manner, with effects appearing after approximately one hour. However, in the past decade it has become evident that corticosteroid receptors also change brain function rapidly. In an extensive series of studies we have shown that cognitive function in humans and rodents are accordingly changed in two time-domains. First, within minutes through rapid non-genomic actions (generally involving the MR), enabling organisms to quickly respond to challenging conditions by selecting a simple self-centered strategy geared to survive the situation. And secondly, with a delay of an hour, through GR-mediated gene-dependent pathways, promoting higher cognitive functions, e.g. altruistic choices which are beneficial in the future or linking stress-related information to the relevant context.
An appropriate balance between these systems is important in health and disease. For instance, down-regulation of the MR – as seen with ageing or after early life stress – is associated with higher prevalence of depression and in rodents leads to cognitive deficits. Conversely, overexpression of MR in rodents appears to protect against cognitive deficits after early life adversity. Current research is focused on effective intervention strategies around puberty, to restore the MR:GR balance and remediate effects of early life stress.

DOI: 10.1530/endoabs.50.PL6

Clinical Endocrinology Trust Visiting Professor Lecture

PL7

Treatment of radioactive iodine refractory thyroid cancer

Martin Schlumberger
Gustave Roussy, Villejuif, France.

Refractory thyroid cancer is rare (4–5 cases/million population/year) and is responsible for most thyroid cancer related death. It includes patients with at least one tumor focus that does not concentrate radioiodine (RAI) or who progress within one year after RAI treatment despite uptake in all lesions. Treatment consists in levothyroxine to maintain a low TSH level and focal treatment modalities (surgery, EBRT, thermo-ablation). In case of multiple metastases with demonstrated RECIST progression, systemic treatment may be indicated. Toxicity is high with a decrease in quality of life and the decision to initiate a treatment is validated by a tumor board.

Cytotoxic chemotherapy is poorly effective. Two anti-angiogenic TKIs, sorafenib and lenvatinib, are labeled by EMA and FDA. Lenvatinib is particularly effective: PFS is prolonged by 15 months, ORR is 65% and OS is improved in elderly patients, and it is used as first line treatment in the absence of contraindication.

However most patients progressed even after CR, and several possibilities can be offered as second line. Other anti-angiogenic drugs have demonstrated some efficacy, including sunitinib, pazopanib and cabozantinib. Intra-tumoral targets such as BRAF or ALK may be present in the tumor tissue, and their presence may lead to use a specific inhibitor.

Redifferentiation by inhibiting the MAPkinase pathway during 4–6 weeks to reinduce RAI uptake in tumor tissue and in that case to treat with RAI may be used in patients with a relatively low tumor burden and with slow tumor progression.

Immunotherapy with check point inhibitors in combination with an anti-angiogenic drug is attractive to improve response rate and duration of response, but no data is currently available.

Despite major achievements in recent years, there is a need for prospective trials, preferably in the frame of networks.

DOI: 10.1530/endoabs.50.PL7

British Thyroid Association Pitt-Rivers Lecture

PL8

Deiodinases and the control of intracellular T3 concentrations

Domenico Salvatore
University of Naples “Federico II”, Naples, Italy.

Thyroid hormone is a major determinant of tissue functions in vivo. Within the tissues, cells are not passive players in the process of hormonal signaling since they can actively customize hormonal action. Triiodothyronine (T3), the active form of thyroid hormone is produced predominantly outside the thyroid parenchyma secondary to peripheral tissue deiodination of thyroxine (T4), with $<20\%$ being secreted directly from the thyroid. Upon entering the cells via specific transporters, thyroid hormone is modified via the action of selenoenzymes known as deiodinases.

While the type II deiodinase (D2) converts the prohormone thyroxine (T4) to the biologically active T3, the type III deiodinase (D3) converts it to reverse T3, an inactive metabolite. D3 also inactivates T3 to T2, terminating thyroid hormone action. Therefore, deiodinases provides cells with the ability to reduce intracellular thyroid signaling or produce extra amounts of T3. This precise control of the T3-dependent transcriptional program is required by multiple organs and cell systems, including the stem and the neoplastic cells. In this context, the identification of a close connection between thyroid hormones and different signal pathways involved in the control of cell functions suggested that the deiodinases may play a role in the definition of cell biology and physiology in normal and pathological context. Deciphering how all these events are achieved, how the T3 signal is controlled and integrated in stem cells and their niches, and how it can impact on them is essentially unknown and represents a challenge for coming years.

DOI: 10.1530/endoabs.50.PL8

Society for Endocrinology Medal Lecture

PL9

Adipose tissue expandability, lipotoxicity and the metabolic syndrome

Antonio Vidal-Puig
University of Cambridge, Metabolic Research Laboratories,
Wellcome Trust-MRC Institute of Metabolic Science, Cambridge, UK.

The link between obesity and type 2 diabetes is clear on an epidemiological level, however the mechanism linking these two common disorders is not well defined. One hypothesis linking obesity to type 2 diabetes is the adipose tissue expandability hypothesis. The adipose tissue expandability hypothesis states that a failure in the capacity for adipose tissue expansion, rather than obesity per se is the key factor linking positive energy balance and type 2 diabetes. All individuals possess a maximum capacity for adipose expansion which is determined by both genetic and environmental factors. Once the adipose tissue expansion limit is reached, adipose tissue ceases to store energy efficiently and lipids begin to accumulate in other tissues. Ectopic lipid accumulation in non-adipocyte cells causes lipotoxic insults including insulin resistance, apoptosis and inflammation. This talk discusses the links between adipokines, inflammation, adipose tissue expandability and lipotoxicity. Finally, we will discuss how considering the concept of allostasis may enable a better understanding of how diabetes develops and allow the rational design of new anti diabetic treatments.

DOI: 10.1530/endoabs.50.PL9

Society for Endocrinology Jubilee Lecture

PL10

Bacteria, steroids and formyl peptide receptors – more twists to the inflammatory response

Julia Buckingham[1] & Felicity Gavins[2]
[1]Brunel University London, UXBRIDGE, London, UK; [2]Louisiana State University, Shreveport, Louisiana, USA.

Annexin A1 (AnxA1), a Ca^{2+} and phospholipid binding protein, is a mediator of glucocorticoid (GC) action in the neuroendocrine and host defence systems. It acts at least in part via members of the membrane bound formyl peptide receptor (Fpr) family, particularly Fpr2 which is also a target for the anti-inflammatory eicosanoid, lipoxin A_4, as well as pro-inflammatory bacterial formylated peptides. Unregulated inflammation underlies many diseases, including sepsis. Our recent studies have revealed tissue specific roles for the AnxA1-Fpr2 system in the resolution of inflammation in the brain, pituitary gland and adrenal cortex in an animal model of sepsis. They also revealed that this system plays a pivotal role in mediating the profound impairment of adrenocortical function which follows the initial hypersecretion of GCs in this model. These and other data provide further evidence of the complex interplay between endogenous mediators and bacterial peptides in the manifestation and resolution of inflammation.

DOI: 10.1530/endoabs.50.PL10

Society for Endocinology Journal Awards

Society for Endocrinology Journal Award – *Journal of Endocrinology*

JA1

A vital region for human glycoprotein hormone trafficking revealed by an LHB mutation

Iulia Potorac, Adolfo Rivero-Müller, Ashutosh Trehan, Michał Kiełbus, Krzysztof Jozwiak, Francois Pralong, Aicha Hafidi, Albert Thiry, Jean-Jacques Ménagé, Ilpo Huhtaniemi, Albert Beckers and Adrian F Daly

Journal of Endocrinology, 2016 **231** 197–207. **DOI: 10.1530/JOE-16-0384**

DOI: 10.1530/endoabs.50.JA1

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

JA2

MuRF1 mono-ubiquitinates TRα to inhibit T3 induced cardiac hypertrophy *in vivo*

Kristine M Wadosky, Jessica M Berthiaume, Wei Tang, Makhosi Zungu, Michael A Portman, A Martin Gerdes & Monte S Willis

Journal of Molecular Endocrinology 2016 **56** 273–290. **DOI: 10.1530/JME-15-0283**

DOI: 10.1530/endoabs.50.JA2

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

JA3

Social isolation induces autophagy in the mouse mammary gland: link to increased mammary cancer risk

Allison Sumis, Katherine L Cook, Fabia O Andrade, Rong Hu, Emma Kidney, Xiyuan Zhan, Dominic Kim, Elissa Carney, Nguyen Nguyen, Wei Yu, Kerrie B Bouker, Idalia Cruz, Robert Clarke & Leena Hilakivi-Clarke

Endocrine-Related Cancer 2016 **23** 839–856. **DOI: 10.1530/ERC-16-0359**

DOI: 10.1530/endoabs.50.JA3

Society for Endocrinology Journal Award – *Clinical Endocrinology*

JA4

Subcutaneous infusion of kisspeptin-54 stimulates gonadotrophin release in women and the response correlates with basal oestradiol levels

Shakunthala Narayanaswamy, Channa N Jayasena, Noel Ng, Risheka Ratnasabapathy, Julia K Prague, Deborah Papadopoulou, Ali Abbara, Alexander N Comninos, Paul Bassett, Stephen R Bloom, Johannes D Veldhuis & Waljit S Dhillo

Clinical Endocrinology 2016 **84** 939–945. **DOI: 10.1111/cen.12603**

DOI: 10.1530/endoabs.50.JA4

Symposia

Steroids and the Skeleton

S1.1

Abstract unavailable.

S1.2

Skeletal actions of glucocorticoids: Molecular mechanism

Jan Tuckermann
Institute of Comparative Molecular Endocrinology, University of Ulm, Ulm, Germany.

Glucocorticoids have profound effects on bone leading to glucocorticoid-induced osteoporosis observed at long term steroid therapy. The glucocorticoid receptor (GR) is a hormone-induced transcription factor controlling gene expression as a monomer or dimeric molecule. We demonstrated- in contrast to the prevailing view - that the induction of genes by dimeric GR molecules suppresses inflammation in disease models. In contrast the monomer GR mediates inhibition of bone formation and bone loss. Using high content screen analysis, we identified novel modulators that abrogate the deleterious effects of glucocorticoids on bone. Our mechanistic studies provide new drug targets and rationales for improved steroid therapy with lesser side effects.

DOI: 10.1530/endoabs.50.S1.2

S1.3

Skeletal actions of glucocorticoids – *in vivo* models

Claire Wood[1,2]
[1]Roslin Institute, Edinburgh, UK; [2]Institute of Genetic Medicine, Newcastle, UK.

Glucocorticoids are effective for the treatment of many chronic conditions but their use is associated with frequent and wide-ranging adverse effects including osteoporosis and growth retardation. The mechanisms that underlie the undesirable effects of GCs on skeletal development are unclear and there is no proven effective treatment to combat them. An *in-vivo* model that investigates the development and progression of GC-induced changes in bone is, therefore, important and a well characterized pre-clinical model is vital for the evaluation of new interventions.
Currently, there is no established animal model to investigate GC effects on skeletal development and there are pros and cons to consider with the different protocols used to induce osteoporosis and growth retardation. This talk will summarize the literature that is available and highlight the models and techniques employed in experimental studies to date.

DOI: 10.1530/endoabs.50.S1.3

When Receptors Go Rogue

S2.1

Stress and direct targeting of mitochondrial gene expression by the glucocorticoid receptor in the brain

Richard Hunter[1,2]
[1]University of Massachusetts Boston, Boston, Massachusetts, USA; [2]The Rockefeller University, New York, New York, USA.

Glucocorticoids (GC) are involved recruiting the energetic response to stress and act principally via the glucocorticoid receptor (GR). The GR is classically understood to function as a nuclear transcription factor. However, the nuclear genome is not the only genome in eukaryotic cells. The mitochondria also contain a small circular chromosome – the mitochondrial DNA (mtDNA) – that encodes 13 proteins. It has been established that, in the brain and other systems, the GR is translocated from the cytosol to the mitochondria and that stress and corticosteroids have a direct influence on mtDNA transcription and mitochondrial physiology. To determine if stress affects mitochondrially transcribed mRNA (mtRNA) expression we exposed adult male rats to both acute and chronic immobilization stress and examined mtRNA expression using quantitative RT-PCR. We found that acute stress had a main effect on mtRNA expression and that expression of the ND-1, ND-3, ND-6 and ATP-6 genes was significantly down-regulated. Chronic stress induced a significant up-regulation of ND-6 expression. Adrenalectomy abolished acute stress-induced mtRNA regulation, demonstrating GC dependence. ChIP Sequencing of GR showed that corticosterone treatment induced a dose-dependent association of the GR with the control region of the mitochondrial genome. Further work has shown that GCs regulate mtRNA expression in a number of brain regions and peripheral tissues. These findings demonstrate GR and stress-dependent transcriptional regulation of the mitochondrial genome in vivo and are consistent with previous work linking stress and GCs with changes in the function of brain mitochondria.

DOI: 10.1530/endoabs.50.S2.1

S2.2

Dissecting thyroid hormone receptor action

Lars Moeller
University of Duisburg-Essen, Essen, Germany.

Thyroid hormone (TH) and TH receptors (TRs) α and β are currently perceived as prototypical nuclear receptors, acting by binding to TH response elements (TREs) in regulatory regions of target genes. This nuclear signaling is long established as the canonical pathway for TH action. However, TRs can also act non-canonically, independent from DNA binding and outside the nucleus, by modulating second messenger signaling *in vitro*. Whether such non-canonical TR action is relevant *in vivo* has so far been unknown. The main reason is that the physiological role of TRs has been studied *in vivo* for more than fifteen years by comparing WT mice with TR knockout (TR KO) mice. Since canonical and non-canonical TR signaling are both present in WT and absent in TR KO mice, such a comparison could not distinguish between the two mechanisms. To solve this problem and separate both modes of TH/TR signaling, we abolished DNA-binding of TRs in TRαGS and TRβGS mice. We show that several important physiological TH effects are preserved despite disrupted TR DNA-binding, most notably heart rate, body temperature, blood glucose and triglyceride concentration, all of which were regulated by non-canonical TR signaling. Additionally, we confirm that TRE-binding defective TRβ leads to disruption of the hypothalamic-pituitary-thyroid axis with resistance to TH, while mutation of TRα causes a severe delay in skeletal development, showing TRE-mediated and tissue-specific canonical signaling. These results provide *in vivo* evidence that non-canonical TR signaling exerts important cardiometabolic effects, which are clearly separated from canonical actions. Consequently, these data challenge the current paradigm that TH action is exclusively mediated through regulation of gene transcription at the nuclear level.

DOI: 10.1530/endoabs.50.S2.2

S2.3

Extra-nuclear estrogen receptors in breast cancer

Ellis Levin
University of California, Irvine, Irvine, USA.

Steroid receptors (SR) respond to binding of their ligands with rapid signal transduction resulting from engaging extra-nuclear receptors. This occurs in addition to the conventional aspects of steroids/nuclear SR that regulate gene transcription. In breast cancer, estrogen and progesterone receptors (ER, PR) are present at the plasma membrane in addition to the nucleus. Here the receptors activate many pathways as G-protein coupled receptors, resulting in epigenetic and genetic contributions to nuclear ER action, as well as post-translational modifications of proteins, altering their functions. In breast cancer, this impacts metabolism that fosters adaptation to changing glucose availability in these highly glycolytic tumors. Signaling through ERK, PI3K-AKT-mTor and other pathways stimulates proliferation, survival, and epithelial cell migration/invasion. ER alpha and beta also exist in the mitochondria of breast cancer cell lines, where they modulate the responses to endocrine therapies, and are potential therapeutic targets in aggressive breast cancer. Activating mutations of ERalpha in endocrine resistant tumors also function through signal transduction. The importance of

extra-nuclear ER in many developmental and functional aspects is established but targeting these cellular pools of receptors in malignancy is under development.

DOI: 10.1530/endoabs.50.S2.3

Fat and Fertility

S3.1

Obesity, fertility and pregnancy

Rebecca Reynolds
University of Edinburgh, Edinburgh, UK.

Rates of among women of reproductive age are rising such that 1 in 5 women in the UK are obese at antenatal booking. Female obesity is associated with reduced fertility including ovulatory dysfunction and increased time to pregnancy. Obese pregnancy is associated with increased pregnancy loss and stillbirth, and with increased risk of major pregnancy complications including gestational diabetes and preeclampsia. In addition there are short and long-term complications for the offspring including macrosomia, shoulder dystocia and risk of later obesity and cardiometabolic disease. Results of intervention studies to improve fertility rates and reduce pregnancy complications in obese women will be discussed including weight loss and lifestyle interventions, bariatric surgery and pharmacological interventions such as metformin. Considerations for optimal management of obese women prior-to and during pregnancy will be discussed, drawing upon our own experience from running an antenatal metabolic clinic for very severely obese women (BMI $>$ 40) and from the evidence presented in our recently developed Royal College of Obstetrics and Gynaecology Green Top Guideline for management of obese pregnancy.

DOI: 10.1530/endoabs.50.S3.1

S3.2

Abstract unavailable.

S3.3

Abstract unavailable.

Pituitary Disease in Adolescents

S4.1

Hypothalamic and pituitary stalk lesions in adolescents

Joanne Blair
Alder Hey Children's Hospital, Liverpool, UK.

Lesions of the hypothalamus and pituitary stalk are rare in adolescence. Congenital and acquired, benign and malignant lesions occur, and the spectrum of diagnoses differs from that in adults, with inflammatory conditions occurring less frequently.

Lesions that develop in the hypothalamus may extend to the pituitary and present with features of pituitary hormone deficiencies, including arrest of growth and puberty in the adolescent age group, or visual disruption. Diabetes insipidus is more likely to be present at diagnosis of hypothalamic tumours than in patients with primary pituitary lesions. Features of raised intracranial pressure may be present if the foramen of Monroe is obstructed. The hypothalamic syndrome of morbid and escalating obesity, disruption of the sleep wake cycle, adipsia, temperature dysregulation and cognitive and behavioural disturbance may be present at diagnosis, or develop following treatment, and is especially challenging to manage. Developmental abnormalities that impinge on the pituitary stalk include Rathke's cleft cysts, epidermoid and arachnoid cysts. Incidental findings of pituitary stalk thickening on an MRI performed for unrelated reasons pose a particular challenge, as normative data for the dimensions of the pituitary stalk in childhood and adolescence are not robust, and biopsies of the pituitary stalk may readily disrupt pituitary function. Neoplastic lesions of the pituitary stalk are more likely to be present in patients with diabetes insipidus, and in this age group the most common diagnoses include germ cell tumours and Langerhans cell histiocytosis. Lymphoma may also develop in this region.

In this talk we will use clinical cases to consider the challenges of diagnosis and management of young people with tumours in these regions.

DOI: 10.1530/endoabs.50.S4.1

S4.2

Abstract unavailable.

S4.3

Prolactinomas in adolescents

William Drake
St Bartholomew's Hospital, London, UK.

Lactotroph pituitary adenomas (prolactinomas, PRLomas) are the most common form of functioning pituitary tumour. The vast majority can be managed successfully by means of medical (dopamine agonist) therapy; only a small minority require second-line therapy of surgical resection with or without adjunctive radiation. PRLomas occur in adolescent patients, but are unusual. Using a combination of illustrative case presentations and selective reference to informative publications, this talk will explore clinical differences in the assessment and treatment of PRLomas in adolescent patients.

DOI: 10.1530/endoabs.50.S4.3

Beyond Paragangliomas

S5.1

SDH mutations in tumourigenesis

Eamonn Maher
University of Cambridge, Cambridge, UK.

Seventeen years ago, germline mutations in the *SDHD* gene were reported to be associated with familial head and neck paraganglioma (HNPGL) and, subsequently, sporadic and familial phaeochromocytoma and paraganglipoma (PPGL). Thereafter germline mutations in other succinate dehydrogenase subunit genes (*SDHB, SDHC, SDHA*) were also found to predispose to HNPGL and PPGL. Succinate dehydrogenase has critical roles in the Krebs cycle and respiratory chain electron-transport (as part of mitochondrial complex II) and disease associated germline SDH subunit (*SDHx*) mutations are loss of function mutations with SDH-associated tumours demonstrating biallelic inactivation of the relevant *SDHx* subunit. SDH-mutated tumours show increased expression of hypoxia-inducible genes, and genomic and histone hypermethylation and these effects appear to result, in part, through succinate-mediated inhibition of α-ketoglutarate-dependent dioxygenases. Though the range of tumours associated with *SDHx* has expanded beyond HNPGL/PPGL to include renal cell carcinoma, gastrointestinal stromal tumours (GIST) and pituitary adenomas-associated tumours, the lifetime tumour risks in individuals who carry a germline *SDHx* mutation are significantly lower than originally described raising questions about the optimum screening protocol for asymptomatic mutation carriers. Characterisation of germline *SDHx* mutations clarifies inheritance patterns (all are inherited in an autosmal dominant trait but SDHD mutations generally only cause disease

when paternally inherited), malignancy risk (high with *SDHB* mutations) and risk for specific tumour types (this varies according to the SDHx subunit involved and may vary with specific *SDHD/SDHB* mutations). Though further progress is required in our knowledge SDH-related tumourigenesis and for personalised tumour risk prediction and management, SDHx mutation analysis is now routine in patients with PPGL, HNPGL and wild-type GIST and SDH-associated neoplasia provides a paradigm for investigating the role of disordered cellular metabolism in tumourigenesis.

Review: Baysal B E, Maher E R. Endocr Relat Cancer. 2015;22:T71-82

DOI: 10.1530/endoabs.50.S5.1

S5.2

Identification of novel therapeutic targets in SDH-mutated cancers: tracing dysfunction

Charlotte Lussey-Lepoutre[1,2,3], Kate E R Hollinshead[4], Christian Ludwig[4], Melanie Menara[1,2], Aurelie Morin[1,2], Anne-Paule Gimenez-Roqueplo[1,2,3], Judith Favier[1,2] & Daniel A Tennant[4]

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Since the discovery of mutations in succinate dehydrogenase (SDH) complex early this century, it has been shown that tumours underpinned by deficiencies in this metabolic enzyme will demonstrate altered cell metabolism. However, the precise nature of these changes remains poorly described. The metabolic network within cells is highly redundant, with multiple pathways capable of synthesising the required building blocks for cell growth. By the very fact that SDH-deficient cells form tumours, we know that cells have found a way around this mutation. However, it is likely that this metabolic re-wiring has compromised their redundancy. Investigations that pinpoint the enzymes required in the SDH-deficient metabolic network may therefore lead to the identification of novel specific targets for tumours with SDH mutations.

Aspartate is a key amino acid, required for the synthesis of all nucleotides and proteins – its synthesis is therefore critical for cellular anabolism. We recently showed that cells lacking Sdhb are deficient in aspartate – a direct consequence of loss of SDH activity. SDH-deficient cells instead become reliant on the activity of pyruvate carboxylase (PC), a mitochondrial enzyme, for the majority of aspartate synthesis. We therefore showed that knockdown of PC activity results in lethality in SDH-deficient cells but has little effect on wild-type cells.

Interestingly, we have also observed perturbations in the metabolism of other amino acids, including proline and alanine, suggesting that there may be multiple opportunities for novel therapeutic targets through the investigation of this class of metabolites.

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S5.3

Surveillance imaging strategies in SDHx

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The increased testing for key genes associated with familial paraganglioma syndromes has, in turn, led to a rapid increase in the identification of asymptomatic carriers through cascade screening. Mutations in SDH subunits B and D account for approximately 50% of the 'gene positive' index case results, yet there remains significant controversy and variability with respect to the screening strategies for their asymptomatic relatives. For SDHD at risk carriers, surveillance imaging strategies should aim to identify tumours early in order that morbidity is minimised, by intervening with the correct mode of treatment at the appropriate time. SDHB gene mutations pose a particular problem due to the dichotomy between a relatively low penetrance and a relatively high rate of malignant transformation. Reliable surveillance imaging strategies for SDHB require both a modality and a frequency of imaging that aims to prevent the occurrence of metastatic SDHB related disease, whilst minimising the impact and potential harm to the individual.

DOI: 10.1530/endoabs.50.S5.3

Sex Hormones Through the Ages

S6.1

Menopause guidelines: theory to practice

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The Guideline 'Menopause: Diagnosis and Management' was published by the National Institute of Health and Care Excellence (NICE) in the UK in November 2015, the aim being to improve the knowledge level of both health care professionals and their patients regarding the menopause and to standardise care across the UK. Recommendations were developed following the systematic review of the current evidence-base. Each review question posed (17 in all) was subject to systematic review and meta-analysis and appropriate recommendations written by a multidisciplinary group.

Recommendations were made on:

- Individualised care.
- Diagnosis of perimenopause and menopause.
- Information and advice.
- Managing short-term menopausal symptoms (a full range of treatments).
- Long-term benefits and risks of hormone replacement therapy (HRT).
- Diagnosing and managing premature ovarian insufficiency (POI).

The aim of the guidelines is to give the woman and her doctor as much information and explanation as possible in order to achieve the best individualised care. This should enable her to make an evidence-based choice. There are sections on a 'normal' menopause, specific recommendations for women with POI, and women with vasomotor or other menopausal symptoms for whom standard HRT is contraindicated (e.g. those with breast cancer). This presentation will cover benefits and risks of HRT, diagnosing and managing premature ovarian insufficiency and diagnosis of natural menopause.

Since publication there has been considerable publicity with the development of Quality Standards by NICE against which care can be audited, and which can be used to commission services in the community. With the aid of the media, more women are becoming aware and the level of knowledge of some GPs is improving. As always this is a slow process but increased awareness of menopause and its implications is vital for the doctors and their patients.

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S6.2

Brain Mechanisms for the Metabolic Control of Puberty

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Puberty is a major developmental event in the life-course of any individual that is under the control of sophisticated regulatory networks, which integrate central and peripheral signals, as well as environmental cues. Among its numerous modifiers, puberty is highly sensitive to metabolic signals, and different metabolic stressors, ranging from subnutrition to morbid obesity, are known to have a discernible impact on the tempo of puberty, which might have a durable impact on disease risk and health status later in life. While the neuroendocrine substrate for the metabolic gating of puberty remains ill defined, our knowledge of the mechanisms whereby whole body metabolism and pubertal timing are tightly connected has recently expanded significantly. This has been due, to a large extent, to the discovery of the pubertal impact of key metabolic hormones, epitomized by the permissive role of leptin on puberty onset, as well as the identification of the key roles of the neuropeptide, kisspeptin, in the precise control of pubertal timing; a function that seemingly includes an important role as relay for the metabolic regulation of puberty. In this presentation, we will briefly summary these recent developments and will focus our attention on recent findings illustrating the roles of brain circuits involving cellular energy sensors, such as AMPK, and neuropeptide partners of kisspeptin, such as neurokinin-B and melanocortins, in the integral regulation of body weight homeostasis, metabolism and puberty.

DOI: 10.1530/endoabs.50.S6.2

S6.3

The genetics of delayed puberty

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The genetic control of puberty remains an important but mostly unanswered question. Late pubertal timing affects over 2% of adolescents and is associated with adverse health outcomes including short stature, reduced bone mineral density and compromised psychosocial health. Self-limited delayed puberty (DP) is a highly heritable trait, which often segregates in an autosomal dominant pattern; however, its neuroendocrine pathophysiology and genetic regulation remain unclear. Using whole and targeted exome sequencing in individuals from our large, well-phenotyped cohort with self-limited DP, we have identified key candidate genes relevant to the pathogenesis of DP. To date the functional consequences of potentially pathogenic variants identified by our lab in 3 candidate genes have been interrogated via tissue expression studies, *in vitro* assays and utilising animal models. Our strategy, together with what is known from published literature, has highlighted that the pathogenesis of DP is likely to be heterogenic. Several pathways have been implicated to date, including: abnormalities of GnRH neuronal development and function, GnRH receptor and LH/FSH abnormalities, metabolic and energy homeostasis derangements and transcriptional regulation of the HPG axis.

DOI: 10.1530/endoabs.50.S6.3

S7.2

Abstract unavailable.

S7.3

Kisspeptin and the control of reproductive behaviour

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A decade of study has conclusively shown that the reproductive hormone kisspeptin is a critical regulator of the HPG axis acting in the hypothalamus to control GnRH secretion. More recently, the role of kisspeptin outside the HPG axis has received increasing attention with the emergence of associations between kisspeptin, brain processing and behaviour. In this talk, I will provide evidence from studies in rodents to humans, that collectively demonstrate that kisspeptin can integrate reproductive and emotional behaviour with the control of the HPG axis. These findings have important clinical implications for the treatment of patients with related conditions.

DOI: 10.1530/endoabs.50.S7.3

Taking a Risk on Love – The Endocrinology of Behaviour

S7.1

Risky business – when endocrinology takes over…

Mark Gurnell
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The financial markets represent the largest and most intense competitive forum ever constructed. Here, according to classical economic theory, competition drives optimal allocation of capital to projects with the highest returns, thereby promoting global prosperity. However, financial markets can be volatile, cycling between 'bull' and 'bear' states, and threatening the stability of the global economy.

Bull markets can morph into bubbles, in which investors display 'irrational exuberance' (an unrealistic assessment of expected returns); in contrast, bear markets may segue into financial crises, in which investors display 'irrational pessimism' (an almost complete aversion to risk). During bubbles and crashes investors react to price changes in a manner which is precisely the opposite to what economics would predict: the higher securities' prices rise, the more investors buy them; the lower prices fall, the more investors shun them.

We have examined the potential for physiology-induced shifts in risk preferences to influence market stability on the world's trading floors. Our findings show that when uncertainty, represented by market volatility, increases, traders experience a sustained increase in cortisol levels. Using a double-blind placebo-controlled cross-over design, in volunteers who were incentivised to make financial choices, we have shown that a comparable, modest rise in cortisol levels is sufficient to render individuals significantly more risk averse. Our findings point to an alternative model of risk taking in which risk preferences are not stable, but highly dynamic. Such a model might explain why the risk premium on equities rises and falls with volatility, and why the appetite for risk among the financial community expands during a rising market, and contracts during a declining one. Critically, if cortisol responds to increases in uncertainty and volatility, and volatility rises during a financial crisis, then risk taking may decrease just when the economy needs it most.

DOI: 10.1530/endoabs.50.S7.1

Adrenal – In Health and Disease

S8.1

Reshaping the adrenal cortex: the process of adrenarche

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In humans, adrenarche represents a unique endocrine process manifest by the development of the adrenal zonal reticularis and its production of a group of steroids often called the 'adrenal androgens'. The physiologic manifestations of adrenarche are reflected by enhanced dehydroepiandrosterone sulfate (DHEA-S) production and the onset of adult body odor, mild acne and axillary and/or pubic hair. Clinically, the early rise in adrenal androgens is termed premature adrenarche (PremA) and can be characterized by pubic hair development before age 8/9 years in girls/boys. PremA has gained attention in recent years as a possible precursor for hyperandrogenic and insulin-resistant states in adolescence and adulthood. Interestingly, the adrenarche biochemical marker DHEA-S has little or no androgenic activity suggesting that its peripheral conversion or adrenal production of more bioactive steroids is key to the phenotypic effects seen during this process. We have applied histologic, genomic and steroid biome analyses to better define the adrenal changes associated with and the steroids produced during adrenarche. Transcriptome comparison of adrenal zona fasciculata and reticularis defined a unique steroidogenic phenotype for both zones. The expression pattern of key steroidogenic enzymes particularly tracked with adrenarche reticularis expansion and their expression pattern explains the onset of DHEA-S production. Analysis of steroids in children progressing through adrenarche and children with PremA demonstrated changes, not only in DHEA-S, but broad-based alterations in the steroid metabolome coinciding with an apparent infant to adolescent reshaping of the adrenal glands. The steroid changes observed during adrenarche were also significantly exaggerated in Prem-A. This presentation will provide an update of findings related to the intra-adrenal changes seen and the steroids produced during adrenarche.

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S8.2

ACTH signalling and resistance

Li Chan
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The melanocortin-2-receptor (MC(2) receptor), also known as the ACTH receptor, is a critical component of the hypothalamic-pituitary-adrenal axis. The importance of MC(2) receptor in adrenal physiology is exemplified by the condition familial glucocorticoid deficiency (FGD), a potentially fatal disease characterised by isolated cortisol deficiency. MC(2) receptor mutations cause ~25% of cases. The discovery of a MC(2) receptor accessory protein MRAP, mutations of which account for ~20% of FGD, has provided insight into MC(2) receptor trafficking and signalling. MRAP is a single transmembrane domain accessory protein and a critical component of the hypothamo–pituitary–adrenal axis. MRAP is highly expressed in the adrenal gland and essential for ACTH receptor expression and function. We have recently generated *Mrap* knock out mice to study the pathophysiology of ACTH resistance. $Mrap^{-/-}$ mice recapitulates the human FGD phenotype with isolated glucocorticoid deficiency. The work also highlights the importance of ACTH and MRAP in adrenal capsular morphology and cortex zonation.

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S8.3

Genomic approach to management of adrenal tumours

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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 further mechanistic concepts. 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.50.S8.3

Obesity for the Endocrinologist

S9.1

New drug therapies for obesity: Do they work?

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Obesity is a chronic disease associated with a number of co-morbidities. Management options include lifestyle changes, pharmacotherapy and bariatric surgery. European guidelines recommend the use of pharmacotherapy for BMI $\geq 30\,kg/m^2$ or BMI $\geq 27\,kg/m^2$ with comorbidities in adjunct to lifestyle modification. Until 2015, orlistat was the only available medication for the treatment of obesity in Europe. Since then, further pharmacological agents have been approved, including the GLP-1 agonist liraglutide 3 mg (Saxenda) and the combination of Naltrexone/Bupropion (Mysimba). In the USA, the repertoire of approved drugs is more extensive, and includes drugs such as the $5HT_{2C}$ receptor agonist Lorcaserin (Belvic) and the combination of Phentermine/Topiramate (Qsymia). Each of these medications has a unique mode of action and promotes weight loss by targeting hunger and satiety pathways in the brain. The lecture will review mode of action, efficacy and side effects of these new pharmacotherapies. Clinical trial data will be shown to discuss how early response to pharmacotherapy can be predictive of clinically meaningful weight loss long-term for remission of obesity related co-morbidities. New potential pharmaco-therapies based on GLP-1/glucagon receptor co-agonism will be briefly discussed.

DOI: 10.1530/endoabs.50.S9.1

S9.2

Brain control of appetite

Lora Heisler
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Obesity has emerged as one of the key health concerns of this century due to its prevalence and resistance to treatment. Specifically, more than 60% of people within the UK are currently overweight or obese. Recently, significant progress has been made in clarifying brain neurochemicals and regions regulating energy intake and energy expenditure. Among these neurochemicals is the precursor polypeptide pro-opiomelanocortin (Pomc) localised within the homeostatic brain region the arcuate nucleus of the hypothalamus (ARC). A new medication for obesity treatment named lorcaserin was recently launched in the USA. However, mechanism through which lorcaserin's therapeutic benefit is achieved remained to be clarified. Using a combination of viral and genetic technology, we uncovered the specific brain circuits through which lorcaserin reduces food intake. We reveal that lorcaserin suppresses appetite via action at Pomc neurons signaling to melanocortin4 receptors. These findings illustrate that the brain circuits controlling appetite may be pharmacologically harnessed to improve obesity and health.

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S9.3

Abstract unavailable.

Thyroid Cancer – What's Hot What's Not

S10.1

Game changers in the clinical management of thyroid cancer

Bryan McIver
Moffitt Cancer Center, Tampa, FL, USA.

There is increasing recognition that Thyroid Cancer represents a group of diseases with a broad spectrum of malignant behavior, ranging from the indolent papillary microcarcinoma carrying essentially no risk to the patients' health of life; to Anaplastic Thyroid Cancer, the most aggressive human malignancy. The majority of our patients lie between these two extremes and their clinical management must increasingly be predicated on the threat that the disease represents to the patient. This 'Precision Medicine' approach to thyroid cancer management is supported by an increasing weight of evidence, based on improved understanding of the genetic underpinnings of thyroid cancer; long-term studies of outcomes following surgery, radioactive iodine and TSH suppression therapy; and, increasingly, clinical trials of systemic therapy and targeted therapy. True current 'game changers' in the management of thyroid cancer include:

1. Improved diagnostics based on standardized cytopathology reporting; integration of clinical, radiological, cytological and molecular information;
2. Tailored surgical approaches, ensuring that the 'punishment fits the crime', offering active surveillance for the lowest risk cancers; lobectomy; total thyroidectomy; and more extensive dissections where these are necessary;
3. Improved understanding of the role of Radioactive Iodine administration;
4. Evidence-based surveillance and monitoring algorithms;
5. Use of systemic therapy for advanced and progressive thyroid cancer; and
6. The recognition that clinical trials are not only possible, but are essential for continued improvements in our cost-effective, patient-centric management of thyroid cancer.

This presentation will review the evidence basis for a true precision medicine approach to thyroid cancer diagnosis and management, and will highlight areas where International Guidelines are likely to continue to evolve to support this approach.

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S10.2

Improving radioiodine uptake in thyroid cancer through NIS induction

Vicki Smith
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Radioiodine is a central treatment modality for differentiated thyroid cancer. Whilst its utility for post-surgery ablation in some patients remains controversial, the importance of radioiodine in the treatment of recurrent and metastatic disease is clear. Advanced disease which no longer takes up radioiodine (radioiodine-refractory DTC (RR-DTC)) is commonly associated with a poor prognosis, with 10-year survival rates for metastatic RR-DTC $<10\%$. Although new systemic therapies for RR-DTC look promising in clinical trials, the development of drug resistance and significant toxicities highlights the ongoing requirement for alternative strategies. One such strategy is the restoration of radioiodine uptake to enable effective radioiodine treatment. Exploring this approach has emphasised a need to understand exactly how radioiodine uptake, mediated by the sodium iodide symporter (NIS), is regulated and how it is repressed in RR-DTC. NIS expression is downregulated in thyroid cancer, particularly in RR-DTC, and recent approaches have focused on the reinduction of NIS expression using redifferentiation agents such as retinoids or through inhibition of the MAPK pathway, the latter resulting in encouraging clinical trial outcomes. Correct targeting of NIS to the plasma membrane is also essential for efficient radioiodine uptake. Our work identified the first known molecule to interact with NIS and modulate its function. Pituitary tumor-transforming gene-binding factor (PBF) binds NIS and induces its internalisation. This interaction is mediated by PBF phosphorylation by Src kinase and Src inhibitors prevent PBF-mediated repression of NIS. We continue to evaluate the potential clinical utility of Src/PBF inhibition in restoring radioiodine uptake and are currently investigating two further novel interactors of NIS which modulate its function; ADP-ribosylation factor 4 (ARF4) and valosin containing protein (VCP). Taken together, a combination of drug treatments that induce both NIS expression and membrane localisation is likely to be required for maximum restoration of radioiodine uptake in RR-DTC.

DOI: 10.1530/endoabs.50.S10.2

S10.3

Molecular mechanism of thyroid tumourigenesis

Pilar Santisteban
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Thyroid cancer remains the most common endocrine malignancy worldwide and its incidence and mortality has increased steadily over the last four decades. In general terms it has a good outcome, however, some patients develop aggressive forms of thyroid cancer that are untreatable and the molecular bases are poorly understood. These aggressive forms have lost NIS (Na/I Symporter) function, one of the most important hallmarks during thyroid cancer progression as it leads to radioiodine-resistant metastastic disease. Our work has contributed to understand the mechanisms involved in iodide uptake repression and tumor progression. We have found that BRAF decreases NIS expression and impairs NIS trafficking to the membrane of follicular thyroid cells, and accordingly causes (RAI)-refractory metastatic disease in patients with papillary thyroid cancer. We demonstrated that the mechanism by which BRAF impairs NIS function is mediated by a TGFβ autocrine loop. Furthermore by next-generation sequencing and gene expression analysis we have identified a master miRNA (miR) regulatory network involved in essential biological process such as thyroid differentiation. Among those miRs, the most abundantly expressed in thyroid tumors is the miR-146b and we found that it binds to the 3'-UTR region of both PAX8 and NIS, leading to impaired protein translation and subsequently a reduction of iodide uptake. Besides, we show that miR-146b and PAX8 regulate each other sharing common target genes, thus highlighting a novel regulatory circuit that govern differentiated phenotype in thyroid tumors. In conclusion our work has demonstrated novel mechanisms involved in NIS repression that could be exploited therapeutically for improved treatment of advanced thyroid cancer.

DOI: 10.1530/endoabs.50.S10.3

New Developments in Adrenal Hypertension

S11.1

ACTH: an underappreciated driver of hypertension

Eleanor Davies
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Hypertension is one of the most common risk factors for cardiovascular disease and is well known to have a substantial heritable component. The mineralocorticoid aldosterone plays a key role in the regulation of BP and excess production can lead to hypertension. Therefore, much attention has focused on the genes mediating its biosynthesis.

The terminal stage of aldosterone production is catalysed by the aldosterone synthase enzyme, encoded by the *CYP11B2* gene. We have shown that this gene is highly polymorphic and that variation in its regulatory regions associate with altered aldosterone production and hypertension due to changes in transcriptional and post-transcriptional gene regulation. Interestingly, polymorphic variation at two key loci involved in the biosynthesis of cortisol, *CYP11B1* and CYP17A1, are also associated with increased aldosterone production and hypertension.

While the influence of *CYP11B2* expression over aldosterone secretion is obvious, it not immediately clear how *CYP11B1* and *CYP17A1* affect the aldosterone phenotype, given their lack of expression in the aldosterone-producing adrenal zona glomerulosa. However, one hypothesis, which we have long proposed, concerns the role of ACTH. Although often overlooked as a significant long-term regulator of aldosterone, we have evidence that common genetic polymorphisms at this trio of steroidogenic genes affects ACTH secretion and action, with consequences for the aldosterone response. We believe this relationship between ACTH and the biosynthesis of corticosteroids, including aldosterone, is a key factor in the development of hypertension. The relative frequency of the polymorphisms we have identified implies a widespread genetic predisposition to high blood pressure. Therefore, understanding the genetic influences underlying ACTH and its regulation of aldosterone secretion could ultimately lead to improved control of blood pressure and the differential diagnosis of hypertension.

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S11.2

Adrenal vein sampling vs imaging in primary aldosteronism

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Primary aldosteronism (PA) is the most frequent form of secondary hypertension and results in an increased incidence of cardiovascular complications, independent of blood pressure. PA has two main causes: unilateral aldosterone-producing adenoma (APA, Conn's syndrome) and bilateral adrenocortical hyperplasia (BAH). The distinction is important because adrenalectomy for APA has the potential for cure. In order to identify an APA adrenal vein sampling (AVS) is advocated by guidelines. AVS entails selective cannulation of the adrenal veins and sampling of blood of these for determination of aldosterone and cortisol. AVS is technically demanding and expensive and has therefore limited availability. A cheaper and simpler classic alternative to AVS is adrenal CT-scanning but the concordance between AVS and CT-scanning with regard to the presence of an APA is poor. The supposed superiority of AVS for selecting patients for adrenalectomy is mostly based on retrospective studies in which AVS results guided management and in which clinical follow-up was often lacking, all leading to a high risk of bias. We therefore performed a pragmatic randomised diagnostic trial, SPARTACUS (Subtyping PA: a Randomized Trial Comparing AVS and Computed Tomography Scan) in which we used clinical outcomes (antihypertensive medication use, blood pressure, biochemical cure, quality-of-life and costs) to determine the clinical value of AVS and CT in 200 patients with PA. The main findings are that clinical outcomes are similar regardless if AVS or CT is used to guide management. Both tests are imperfect in biochemical cure. Intriguingly the concordance between CT and AVS in the AVS arm was dismal. In my talk I will discuss the importance of the SPARTACUS design for diagnostic problems and the possible explanations for the findings on AVS performance and the potential for improvement. I will also discuss the implications for research and clinical management of PA.

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S11.3

Mechanisms of salt-sensitive hypertension

Matthew Bailey
The University of Edinburgh, Edinburgh, UK.

25–30% of normotensive people have salt-sensitive blood pressure, which is an independent risk factor for cardiovascular mortality. The underlying mechanisms are not clear but impaired renal salt excretion and vascular (endothelial) dysfunction are currently viewed as important processes for salt-sensitivity.

To add complexity, non-modulation of the hierarchical control systems that regulate renal and vascular function are critical to the development of salt-sensitivity. We have used the syndrome of Apparent Mineralocorticoid Excess (AME) as an exemplar system to interrogate mechanisms of salt-sensitivity. This syndrome is caused by loss of function of 11βHSD2, an enzyme which metabolizes cortisol in cells and thereby preventing glucocorticoids from activating the mineralocorticoid receptor. AME is characterised by sodium retention and severe salt-sensitive hypertension. Global knockout of the gene in mice or rats recapitulates human AME, inducing salt-sensitive hypertension, impaired sodium renal excretion and a rapid decline in renal function. Heterozygous knockout mice have normal BP but retain sodium and become hypertensive when fed a high salt diet, analogous to the mild type 2 variant of AME in humans. In each of these studies, aldosterone modulated appropriately with dietary salt but circulating corticosterone increased and the sympathetic nervous system was hyperactive.

We have used a cre-lox strategy to resolve components of salt-sensitivity. Deleting 11βHSD2 throughout the CNS does not change blood pressure *per se* but induces a phenotypic switch from salt-resistance to salt-sensitivity. This transition was amplified by an abnormal salt-appetite: such that ad lib salt-intake was ∼3 times higher than in controls. We are currently examining renal and vascular function in CNS-knockout mice under basal salt intake and after high salt feeding. Our research highlights the physiological complexity of salt-sensitivity, providing evidence for brain-kidney cross talk influenced by the sympathetic nervous system and hypothalamic-pituitary–adrenal axis.

DOI: 10.1530/endoabs.50.S11.3

Early Career Symposia

Alternative career pathways

EC1.1

A career in pharma

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The pharmaceutical industry provides challenging and rewarding career opportunities for physicians. Given that clinical drug development for cardio-metabolic and oncological indications are the focus for many pharmaceutical companies, physicians and scientists with specialist training in endocrinology, diabetes and metabolism are in demand. In addition to responsibilities in clinical trial design, drug safety and regulatory affairs, physician scientists with an intimate knowledge of human disease processes are increasingly sought after to support human drug target validation efforts. In this seminar, the scope of career opportunities and responsibilities for physicians in the pharmaceutical industry will be discussed.

DOI: 10.1530/endoabs.50.EC1.1

EC1.2

A career in teaching or lecturing

Maralyn Druce
Barts and the London School of Medicine and Dentistry, QMUL, London, UK.

Although this is a session on 'Alternative Careers' most of us, whether clinicians or researchers, spend a portion of our working lives teaching others. This may be because we have to or because we want to! Either way, in this short talk we will think about ways to expand your teaching portfolio, and we will look at options for formal roles in teaching and consider how to get recognition and accreditation for your efforts. We will think about ways to build a timetable which integrates teaching with the other types of work that you enjoy, leading to an interesting and rewarding career.

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EC1.3

A career in the charitable sector

Rebecca McIntosh
Wellcome Trust, London, UK.

Since completing a PhD in Developmental Neurobiology at King's College London, I have worked as a Grants Adviser at the Wellcome Trust. Not-for-profit organisations like the Wellcome Trust hold a diverse range of career opportunities for scientists with PhD and post-doctoral experience, from communications to research management. In this short overview talk I'll give an insight into the role of the Grants Adviser, the opportunities for scientists in the charitable sector as well as what the move from the lab into this sector is like.

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EC1.4

A career in publishing

Ian Russell
Bioscientifica, Bristol, UK.

Scholarly publishing is a vibrant industry employing approximately 150 000 people worldwide and generating global revenues of over $15 billion. While it has underpinned scholarly research for more than 350 years it is also an innovative industry that has a strong track record of embracing new technology and business models. Roles are varied including marketing, technology, project and supplier management, commissioning, journalism and scientific writing, editorial development, sales, and business management. Career prospects are good and while scholarly publishers exist in most countries, the USA, UK, Netherlands and Germany each have particularly strong scholarly publishing industries. Many of those recruited to scholarly publishing have degrees in scientific subjects and see publishing as an opportunity to work in an area which continues to offer close contact with the research environment. But what sort of roles are on offer, what kind of skill-sets are required, what kind of career path could you expect, and what do you need to do to get your first job in publishing?

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EC1.5

A career in public health – Leaving the lab to influence individual, community and population health at local, national and international levels

Mike Brannan
Public Health England, London, UK.

Public health is *"the science and art of promoting and protecting health and well-being, preventing ill-health and prolonging life through the organised efforts of society"*. It encompasses a broad range of professionals across the sub-specialisms of health improvement, health services and health protection who meld scientific rigor with practical approaches to improve the health of the population and reduce inequalities across society. In many ways public health is amongst the oldest of health disciplines, with the understanding of how the environment and behaviours impact on individual and population health preceding modern medicine. As a science modern public health has its foundations in the mid-nineteenth century when Edwin Chadwick made the association between a lack of sanitation and disease and mortality. However despite its illustrious history and the huge population health gains through public health (e.g. vaccination, control of communicable disease, tobacco control) it is seldom a career that scientist aspire to or have even heard of. This presentation will explain the types or roles available within public health and how a biochemist found his way from the lab and a career as a public relations consultant to develop a 'third' career in public health. It will explain how public health offers scientists an opportunity to utilise their capability for scientific thinking working with professionals from across disciplines (e.g. politics, communications, healthcare, planning, etc.) in work that engages and builds local communities to improve individual, community and population health.

DOI: 10.1530/endoabs.50.EC1.5

Clinical Management Workshops

Workshop 1: Collateral Damage of Cancer Treatment

CMW1.1

Ovarian function after chemotherapy

Richard Anderson
University of Ediburgh, Edinburgh, United Kingdom.

Chemotherapy and radiotherapy can both cause ovarian failure, and radiotherapy can also damage the uterus increasing the risk of miscarriage and premature delivery. Alkylating agents are recognised to be the most gonadotoxic class of chemotherapeutic agents, but treatment regimens often involve multiple drugs complicating assessment of effect and risk. The prepubertal reproductive system is also sensitive to these effects, although age, with treatment regimen, are important determinants of the degree of effect. Many of the larger studies use amenorrhoea as the key outcome of cancer treatment, with fertility less frequently assessed although there are now data from larger studies after childhood cancer. Premature ovarian insufficiency is also an important outcome, highlighting issues related to the loss of estrogen production as well as shortening of reproductive lifespan.

The explosion in clinical activity surround fertility preservation highlights the need for better individual assessment of risk of loss of post-treatment ovarian function. This involves identification of patient-specific issues, such as the potential impact of her pre-existing ovarian reserve, and extrinsic factors, particularly the treatment she will be receiving, and what fertility preservation techniques are in reality available to her. Pre-chemotherapy ovarian reserve biomarkers such as AMH are predictive of post-chemo ovarian activity in women with breast cancer. The evidence for the efficacy of GnRH analogues to protect ovarian function in early breast cancer is also growing, although the amount of ovarian function saved is likely to be small. Other approaches are also in development to protect ovarian function after chemotherapy, but are largely preclinical at present.

DOI: 10.1530/endoabs.50.CMW1.1

CMW1.2

Abstract unavailable.

CMW1.3

Bone health in cancer survivors

Claire Higham
Christie Hospital, Manchester, United Kingdom.

Cancer and treatments for cancer can have a significant impact on bone health in both children and adults. There are emerging data that bone mineral density is often reduced in survivors of childhood cancers and survivors of both solid tumours and haematological malignancies in adults. Fracture rates in childhood cancer survivors have not been shown to be increased. Older adult cancer survivors, particularly those treated with aromatase inhibitors and androgen deprivation therapy, do have increased fracture rates. This talk will provide an overview of current evidence and guidelines with regards to bone health assessment, monitoring and treatment in both survivors of childhood and adult cancer. The emphasis will be on a practical approach to bone health in an individual patient, taking into account age, imaging, cancer type and treatments received.

DOI: 10.1530/endoabs.50.CMW1.3

Workshop 2: Hyper and Hypocalcaemia

CMW2.1

Difficult hypercalcaemia

Jennifer Walsh
Mellanby Centre for Bone Research, University of Sheffield, Sheffield, United Kingdom.

Challenges of hypercalcaemia can arise in several points in management: In diagnosis (for example differentiating primary hyperparathyroidism from familial hypocalciuric hypercalcaemia), in emergency management (for example poor response to intravenous saline and bisphosphonates), and in elective management (considering which patients are likely to benefit from parathyroidectomy).

This session will use case examples to explore commonly encountered problems, and discuss the evidence and guidance available to support management decisions.

DOI: 10.1530/endoabs.50.CMW2.1

CMW2.2

Familial hypocalciuric hypercalcaemia

Fadil Hannan
University of Liverpool, Liverpool, United Kingdom.

Familial hypocalciuric hypercalcaemia (FHH) is a rare but highly penetrant autosomal dominant condition, which is characterised by lifelong mild-to-moderate hypercalcaemia in association with normal or mildly raised serum parathyroid hormone (PTH) concentrations. FHH is considered to be a benign and asymptomatic condition, which in general requires no specific treatment. However, as this disorder has a similar serum biochemical phenotype to primary hyperparathyroidism (PHPT), FHH patients have been misdiagnosed as having PHPT, and undergone parathyroidectomy, which generally fails to normalize the hypercalcaemia. In clinical practice, FHH is distinguished from PHPT by measurement of the 24-hour calcium to creatinine clearance ratio (CCCR), which is <0.01 in 95% of FHH patients. However, around 10% of PHPT patients may also have a CCCR of <0.01, and therefore the CCCR test may not always reliably differentiate FHH from PHPT. Thus, additional investigations may be required, and these include measurement of serum calcium concentrations in first-degree relatives and DNA sequence analysis of the genes known to cause FHH. Recent studies have shown FHH to comprise three genetically distinct conditions, designated as FHH types 1–3, which are due to germline loss-of-function mutations affecting the *CASR*, *GNA11* and *AP2S1* genes, respectively. Mutations of the *CASR* have been reported in ~65% of FHH cases; whereas *GNA11* and *AP2S1* mutations account for $<5\%$ and ~10% of FHH cases, respectively. FHH types 1 and 2 are in general asymptomatic disorders; however, FHH type 3 may be associated with symptomatic hypercalcaemia, low bone mineral densities and cognitive dysfunction. This presentation will outline the clinical challenges in diagnosing FHH and also describe the different genetic variants of this disorder.

DOI: 10.1530/endoabs.50.CMW2.2

CMW2.3

Abstract unavailable.

Workshop 3: How do I … (1)

CMW3.1

How do I manage . . . . the patient with thyroid dysfunction after immunotherapy?

Daniel Morganstein
Chelsea and Westminster NHS Foundation Trust, London, United Kingdom; Royal Marsden Hospital, London, United Kingdom.

Immunotherapies such as IL-2 and interferon have long been used in the treatment of certain cancers and immune mediated conditions. It has also long been recognised that their use is associated with an increased risk of autoimmune thyroid disease. Recent advances in the use of checkpoint inhibitors, such as ipilimumab and PD-1 inhibitors, in the treatment of a number of common cancers, as well as treatments such as alemtuzumab in multiple sclerosis have dramatically increased the number of patients treated with these immune modulating drugs.

Thyroid dysfunction has emerged as a common adverse event of these therapies. For example, phase 3 trials of Nivolumab and Pembrolizumab in cancers such as

melanoma and renal cell cancer report rates of thyroid dysfunction of around 10%. However, trials report on the basis of symptoms not laboratory abnormalities and real-world data suggests much higher rates of thyroid dysfunction when including all those with abnormal thyroid function tests (up to 50% in patients with melanoma with a combination of Ipilimumab and Nivolumab).
Hypothyroidism is the most common presentation, although many patients develop a thyroiditis with a thyrotoxic phase proceeding hypothyroidism. The thyrotoxicosis rarely requires specific management, although beta-blockers may be required for symptomatic relief, but the hypothyroidism appears to be permanent requiring thyroid hormone replacement. Interestingly the literature reports a rate of thyroid peroxidase antibody positivity of between 30 and 80%, lower than that seen in classic autoimmune hypothyroidism. A similar pattern and frequency of thyroid dysfunction is described with Alemtuzumab. There are also isolated case reports of Graves' disease following immunotherapy.
There is now some evidence that patients who develop thyroid dysfunction may be more likely to have a tumour response, although it remains unclear whether this is a causal relationship or not.

DOI: 10.1530/endoabs.50.CMW3.1

CMW3.2

How do I manage a patient on a bisphosphonate after 5 years?

Nicola Peel
Sheffield Teaching Hospitals, Sheffield, United Kingdom.

Oral bisphosphonate therapy provides the usual first line approach to the treatment of osteoporosis and is associated with relative reduction in fracture risk of approximately 50% at the spine, 30% at the proximal femur and up to 20% at peripheral sites. Fracture risk reduction is maintained over 5 years of treatment and there are data confirming continued efficacy of treatment for up to 10 years in individuals at high fracture risk. Prolonged bisphosphonate treatment has, however, been associated with rare but serious adverse effects including osteonecrosis of the jaw and atypical subtrochanteric femoral fractures.
Reversal of bisphosphonate treatment effect is gradual, with persisting suppression of bone turnover and maintenance of bone mineral density (BMD) for several months after cessation. It is therefore common practice to consider a pause in treatment after 5 years (3 years for IV treatment). The decision whether to pause treatment at this point is made on an individual basis, taking account of patient preference and the balance of risks and benefits. Factors increasing the individual's risk of fracture may lead to the recommendation to continue without a pause. These include advancing age, low BMD, recent fragility fracture, especially of hip or vertebrae, and use of other medication adversely affecting bone eg glucocorticoids, aromatase inhibitors or androgen deprivation therapy.
Patients who continue treatment beyond 5 years should be counselled regarding the rationale and risks of longer term treatment and given advice to minimise risk through maintenance of good dental health and prompt reporting of any symptoms of groin/thigh pain. Patients who stop bisphosphonate treatment should be evaluated to consider re-introduction if new fractures or risk factors arise, or after 2 years off treatment.

DOI: 10.1530/endoabs.50.CMW3.2

CMW3.3

How do I . . . . reconcile inconsistent results in suspected Cushing's?

Niamh Martin
Imperial College, London, United Kingdom.

'Clinicians who have never missed the diagnosis of Cushing's syndrome or have never been fooled by attempting to establish its cause should refer their patients with suspected hypercortisolism to someone who has.' This quote, by Professor James Findling, an expert in Cushing's syndrome, is a reminder of the difficulties in diagnosing Cushing's syndrome. These difficulties in part reflect the increasing incidence of obesity, hypertension and type 2 diabetes. We will be asked to exclude Cushing's syndrome in individuals who have these diagnoses but do not have hypercortisolism. Similarly, there is no clinical sign or biochemical investigation for Cushing's syndrome which has perfect diagnostic accuracy.
Importantly, we can do harm in misdiagnosing Cushing's syndrome. If we delay diagnosis, the patient could experience the negative effects of excess cortisol. However, perhaps more significantly, a diagnosis of Cushing's syndrome will almost inevitably result in surgery for most patients, so we need to be sure that the patient really has Cushing's syndrome.
The 2008 Endocrine Society Clinical Practice Guidelines recommend three first-line investigations for the diagnosis of Cushing's syndrome and these exploit different aspects of cortisol excess; late night salivary cortisol measurement, dexamethasone suppression testing and 24-hour urine free cortisol measurement. This talk will review the accuracy of these investigations and will explore how to proceed when the clinical suspicion of Cushing's syndrome and the results of these investigations don't match up.

DOI: 10.1530/endoabs.50.CMW3.3

CMW3.4

How do I . . . . manage thionamide induced leucopaenia

Tristan Richardson
Royal Bournemouth Hospital, Bournemouth, United Kingdom.

The presentation will start with a review of the relationship with autoimmune thyrotoxicosis and the white cell count. Pre-therapy measurements and on-going measures of checking for leucopenia will be discussed.
The evidence for a temporal effect of the thionamides will be reviewed. This will detail the times for increased vigilance and appropriate standard advice for patients initiating thionamides. Dosing and different thionamides and their potential varying effects will be presented. The pros and cons of switching medications will be analysed and potential alternatives?
The management of acute leucopenia with associated sepsis secondary to thionamides will then be discussed with inpatient management of the acutely unwell leucopenic patient, with personal observations and best practice described. Options for the unresponding patient will be discussed, from an evidence based perspective and presentation of alternate options that may be useful in managing your next patient with thionamide induced leucopenia.

DOI: 10.1530/endoabs.50.CMW3.4

CMW3.5

How do I . . . . investigate and manage a patient with Bartter or Gitleman syndrome?

John Sayer
Newcastle University, Newcastle upon Tyne, United Kingdom.

Bartter and Gitelman syndromes are salt wasting alkaloses. These inherited conditions are the result of impairment of sodium chloride reabsorption in the loop of Henle (Bartter) or distal tubule (Gitelman). Secondary hyperaldosteronism occurs as a direct result of renal salt wasting resulting in hypokalaemia and metabolic alkalosis. The tubular defects seen mimic those of long-term loop (Bartter) or thiazide (Gitelman) diuretic use and urinary calcium levels and serum magnesium levels can be used to help distinguish them. Molecular genetic testing usually provides a definitive diagnosis. Blood pressure is frequently low or normal (at least until mid-adult life). Treatment of patients with salt-wasting alkaloses involves life-long supplementation with sodium chloride, potassium chloride, and magnesium salts, together with potassium-sparing diuretics and non-steroidal anti-inflammatory drugs.

DOI: 10.1530/endoabs.50.CMW3.5

CMW3.6

How do I . . . . implement patient safety alerts for adrenal insufficiency across my institution

Anna Mitchell
Royal Victoria Infirmary, Newcastle upon Tyne NHS Hospitals Trust, Newcastle upon Tyne, United Kingdom.

Steroid-dependent individuals, in particular those with primary adrenal insufficiency, are a vulnerable patient group. They are prone to acute adrenal crisis which is a life-threatening medical emergency requiring immediate recognition and treatment. Among individuals with primary adrenal insufficiency, acute adrenal crisis has a frequency of 6–8 per 100 patient-years. Unfortunately, delays in diagnosis and management are common, constituting an avoidable source of patient harm.

In the UK, the endocrine community has taken important steps in recent times to improve the safety of steroid-dependent patients. These include the publication of the Society for Endocrinology emergency guideline for the management of adrenal crisis in adult patients, the introduction of a pan-European 'Steroid Emergency card' and patient resources including a video series on giving a steroid injection in an emergency.
In Newcastle upon Tyne Hospitals, we have embedded steroid safety teaching and adrenal crisis management into mandatory trust induction, implemented an electronic record-based steroid alert system and set up a hospital-initiated ambulance service registration pathway for steroid-dependent patients. The aim of these interlocking safety measures is to improve patient care and prevent serious clinical incidents.

DOI: 10.1530/endoabs.50.CMW3.6

Workshop 4: Graves' Orbitopathy: A Thyronet/TEAMED

CMW4.1

Improving outcomes in thyroid eye disease - the TEAMeD 5 programme

Colin Dayan
Cardiff University, Cardiff, United Kingdom.

TEAMeD (Thyroid Eye Disease Amsterdam Declaration Implementation Group UK) was established in 2009 to implement the Amsterdam Declaration, which pledged to improve care for people with TED and prevent TED in those at risk. This autumn, TEAMeD is launching 'TEAMeD-5', a campaign to promote better care for patients with, or at risk of TED. This campaign aims to implement 5 key evidence based recommendations in endocrine clinics across the UK.

DOI: 10.1530/endoabs.50.CMW4.1

CMW4.2

Molecular mechanisms of Graves' Orbitopathy

Mohd Shazli Draman
Cardiff University, Cardiff, United Kingdom.

Graves' orbitopathy (GO) or thyroid eye disease (TED) is an autoimmune condition most common in people with hyperthyroid Graves' disease. Severe GO may cause blindness due to optic compression following expansion of the orbital contents. In many patients, the persistent disfigured appearance of the eyes is a source of significant psychological distress and effective treatments are lacking. This has driven efforts to identify novel therapeutic options resulting in progress in our understanding of the tissue remodelling processes underpinning GO. In this lecture, I will describe briefly clinical aspects of GO including signs and symptoms and risk factors. I will explore GO pathogenesis including target autoantigens, regulation of tissue remodelling and tolerance mechanisms. I will also summarise recent trials of non-immunosuppressive therapies in GO.

DOI: 10.1530/endoabs.50.CMW4.2

Workshop 5: How do I … (2)

CMW5.1

How do I follow up a patient with an indeterminate non-functioning adrenal nodule?

Anna Crown
Royal Sussex County Hospital, Brighton, United Kingdom.

Incidentally discovered adrenal nodules are an increasingly common reason for referral into the endocrine clinic. Assessment includes a hormonal work-up to look for endocrine function, and reviewing the size and radiological characteristics of the lesion. Some nodules have benign radiological features (less than 10 HU on an unenhanced CT scan), whilst others are radiologically indeterminate (more than 10 HU). We worry about missing a malignant process. The research data and international guidelines may be subject to both selection bias and fee for service bias. The pre-test probability of malignancy in a patient with no known malignancy is extremely low. The history may provide clues about the possibility that the lesion represents an adrenal metastasis or an adrenal carcinoma. The size of the lesion is also helpful, with more than 4 cm being a cautious cut-off usually accepted as an indication for surgery, and sub-centimetre lesions probably not requiring any further follow-up. A dedicated adrenal CT scan with wash out sequences, and a review of the radiological characteristics of the lesion with a specialist radiologist as part of an MDT assessment, is recommended. There is less evidence at present to support the use of other diagnostic tests in most situations. Growth on follow-up imaging increases the likelihood of malignancy, but this has to be balanced against the risks of radiation exposure and the opportunity cost for the NHS. Patient preference, co-morbidities and frailty will also influence management plans. For radiologically indeterminate non-functioning adrenal nodules, a pragmatic approach to follow-up could include a dedicated adrenal CT scan with wash out sequences, then (if the lesion is still radiologically indeterminate) two follow-up adrenal scans over a 2 year interval from the initial imaging (non-contrast CT, or MRI in under 40s), before the patient is discharged if the lesion remains stable.

DOI: 10.1530/endoabs.50.CMW5.1

CMW5.2

How do I manage a postmenopausal woman asking for testosterone replacement

Helen Buckler
Christie Hospital, Manchester, United Kingdom.

Oestrogens are formed in the ovary from androgen precursors which circulate at a higher concentration in the blood and have a greater production and secretion rate than oestrogens. Although the post menopausal ovary remains a source of testosterone (T) production there is a fall in total circulating androgens with age and this results from a combination of ovarian failure, decreasing adrenal secretion and peripheral conversion.This relative androgen deficiency is greater in women who have had bilateral oophorectomy, where T levels can fall by 50%, and is also present in premature ovarian insufficiency. It can also occur secondary to adrenal insufficiency or to medication such as the contraceptive pill, oestogen therapy and GnRH analogues. Sex hormone binding globulin (SHBG) binds T at such high affinity that only 1–2% of the hormone is free to act on the target cell. An increase in SHBG can result in decreased free T levels. Correlation between T levels and sexual function is unclear and measurement of free T is often not available.There is, however, evidence emerging demonstrating a role for T in normal sexual function, mood, cognitive function, well being, bone and muscle mass. The relationship between sexual desire and T is complex but reduced libido is a common symptom in menopausal women, particularly in surgically menopausal women and premature ovarian insufficiency. Testosterone replacement can improve sexual function and well being and androgenic side effects are uncommon. Unfortunately there are few licensed androgen preparations available for women.

DOI: 10.1530/endoabs.50.CMW5.2

CMW5.3

How do I … approach CVS surveillance in a patient with Turner Syndrome

Claus H Gravholt
Aarhus University Hospital, Aarhus, Denmark.

New international clinical guidelines have just been published, based on an international effort that started with exploratory meetings in 2014 in both Europe and the USA, and culminated with a Consensus Meeting held in Cincinnati, Ohio, USA in July 2016. These guidelines were initiated and developed by ESE in Europe, and by PES in USA, with important contributions from ESHRE, Endocrine Society, ESC, AHA, Society for Endocrinology, and ESPE.
Morbidity and mortality is increased in TS, especially due to the risk of dissection of the aorta and other cardiovascular diseases, as well as the risk of type 2 diabetes, hypertension, osteoporosis, thyroid disease and other diseases.
During the transition period many young females opt out of longitudinal follow-up, probably because they feel well and cannot clearly see the need for continued medical surveillance. However, osteoporosis, diabetes, both type 1 and 2, hypothyroidism, obesity and a host of other endocrinological diseases and conditions are seen more frequently in Turner syndrome in the long term. Hypertension is frequent and can be a forerunner of cardiovascular disease. Congenital cardiovascular malformations are very frequently seen among females with TS and the introduction of imaging techniques such as MRI or CT are necessary in order to enhance care for TS. Clinical follow-up should be

individually tailored depending on the morbidity burden. Prevention, intervention and proper treatment is only just being recognized.
The description of adult life with Turner syndrome has been broadened and medical, social and psychological aspects are being added at a compelling pace. Proper care during adulthood should be optimized and a framework for care should be in place, since most morbidity potentially is amenable to intervention. In summary, Turner syndrome is a condition associated with a number of diseases and conditions which need the attention of a multi-disciplinary team during adulthood.

DOI: 10.1530/endoabs.50.CMW5.3

CMW5.4

How do I manage Adipsic Diabetes Insipidus

Stephen Ball
Central Manchester University Hospitals, Manchester, United Kingdom; MAHSC, Manchester, United Kingdom.

Maintenance of serum sodium and water balance is a key feature of normal physiology; mediated through the regulation of water intake and renal water loss. Adipsic and hypodipsic disorders are characterized by inadequate spontaneous fluid intake due to defects in osmo-regulated thirst. Patients deny thirst and do not drink, despite dehydration and hypovolaemia. The hypothalamic osmoregulation of thirst and Vasopressin (AVP) production are functionally linked, though anatomically discrete and separate. However, because of the close anatomical relationship of the osmo-sensing mechanisms, adipsic syndromes are often associated with defects in osmo-regulated AVP release: Adipsic Diabetes Insipidus (ADI). A number of different forms of ADI have been described. This presentation will cover the pathophysiology and management of ADI, focusing on practical and pragmatic approaches to sustainable care.

DOI: 10.1530/endoabs.50.CMW5.4

CMW5.5

How do I manage hypercalcaemia during pregnancy?

Amir Sam
Imperial College London, London, United Kingdom.

Hypercalcaemia due to primary hyperparathyroidism during pregnancy may be associated with maternal and foetal complications as well as neonatal tetany. Asymptomatic women with mild hypercalcaemia may be managed conservatively. Symptomatic patients or those with severe hypercalcaemia should be offered parathyroidectomy in the second trimester. This session will summarise the current practice in the management of patients with hypercalcaemia during pregnancy at Hammersmith Hospital.

DOI: 10.1530/endoabs.50.CMW5.5

CMW5.6

How do I manage.... myxoedema coma

Antonia Brooke
Royal Devon and Exeter Foundation Trust, Exeter, United Kingdom.

Myxoedema coma is a rare endocrine emergency with reported high mortality. Exact incidence is hampered by no clear consensus on its definition and the huge variability in its presentation. Most patients are not comatose, and have a form of severe, decompensated hypothyroidism. The common clinical features, including poor mentation, hypothermia, haemodynamic instability and lethargy, correlate poorly to degree of biochemical hypothyroidism. Early detection and identifying common precipitants which disrupt homeostasis, is important to reduce length of stay and mortality. The evidence to support steroids, leiothyronine versus levothyroxine, and the use of loading doses of treatment will all be discussed.

DOI: 10.1530/endoabs.50.CMW5.6

Applied Physiology Workshop

Tissue Engineering for Regenerative Medicine in Endocrinology

APW1.1

Reprogramming gastric tissues for insulin production

Chaiyaboot Ariyachet, Jiaqi Lu, Hyunkee Kim & Qiao Zhou
Harvard University, Cambridge, Massachusetts, USA.

Generating functional insulin-secreting cells is a major goal of developing cell therapies for diabetes. Studies have shown that insulin$^+$ cells can be derived from non-beta cells by cellular reprogramming. We carried out a genetic screen in mouse to identify adult cell types amenable for direct conversion to insulin$^+$ cells by a cocktail of reprogramming factors (Ngn3, Pdx1, and Mafa, termed NPM factors). Surprisingly, the antral stomach epithelial cells were found to possess previously unappreciated ability for conversion into functional insulin$^+$ cells. The induced gastric insulin$^+$ cells have molecular and functional hallmarks of pancreatic beta cells, can secrete insulin in response to high glucose, and suppress hyperglycemia in an experimental form of diabetes. Compared with antral stomach, conversion of intestinal tissue to insulin$^+$ cells is less complete partly due to persistence of the intestinal cell fate regulator Cdx2, which serves as a molecular barrier for reprogramming. Importantly, the gastric insulin$^+$ cells can be readily regenerated from gastric epithelium in vivo, thus providing a renewable source of new insulin$^+$ cells.

To evaluate whether human gastric tissues can be reprogrammed into functional insulin$^+$ cells. We generated human antral stomach mini-organs (hGOs) from human embryonic stem cells (hESCs) by step-wise differentiation. The hGOs possess all the major epithelial and mesenchymal cell types of human antral stomach. We genetically engineered the hES cells, and consequently, the hGOs for inducible expression of NPM factors. Our studies showed that hGOs can be transplanted and remain stable in vivo for at least 6 months. Activation of NPM factors led to induction of insulin$^+$ cells in hGOs, insulin secretion into circulation, and amelioration of experimental diabetes. These studies highlight the potential of engineered human stomach mini-organs as a new transplantable material for glycemic control.

DOI: 10.1530/endoabs.50.APW1.1

APW1.2

Reprogramming cells to acquire steroidogenic potential: towards therapy for adrenal insufficiency

Leonardo Guasti
Queen Mary University of London, London, UK.

Adrenal insufficiency is managed by hormone replacement therapy, which is far from optimal; the ability to generate functional steroidogenic cells would offer a unique opportunity for a curative approach restoring the complex feedback regulation of the hypothalamic–pituitary–adrenal axis. Here we generated human induced steroidogenic cells (hiSCs) from fibroblasts, blood- and urine-derived cells through forced expression of Steroidogenic Factor-1 and activation of PKA and LHRH pathways. hiSCs had ultrastructural features resembling steroid-secreting cells, expressed steroidogenic enzymes and secreted steroid hormones in response to stimuli. hiSCs successfully engrafted into the mouse kidney capsule and underwent intra-adrenal differentiation. Importantly, the hypocortisolism of hiSCs derived from patients with adrenal insufficiency due to congenital adrenal hyperplasia was rescued by expressing the wild-type version of the defective disease-causing enzymes. Our study provides an effective tool with many potential applications to study adrenal pathobiology in a personalized manner and opens venues for the development of precision therapies.

DOI: 10.1530/endoabs.50.APW1.2

APW1.3

3D-Bioprinting coming of age-from cells to organs

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Yale School of Sugery, New Haven, Connecticut, USA.

Over the past decade, annual spending on pharmaceutical development to treat many endocrinological systems has increased exponentially. At the same time, in spite of these huge sums invested, the average number of drugs being approved for human use has decreased to one in ten. Currently, preclinical studies to test the safety and efficiency of new drugs, use laboratory animals and traditional 2D cell culture models. Neither of these methods are completely accurate reflections of how a drug will react in a human patient. A solution has emerged in the form of 3D-Bioprinting technology, developed for the scalable, accurate and repeatable deposition of biologically active materials. With advances in this biomanufacturing technology, durable biological tissues for use in testing new pharmaceutical products are now being harnessed and refined. Going forward, 3D-Bioprnting is being explored as a method for the creation of more advanced structures. In the longer-term, this technology offers the potential to fabricate organised tissue constructs. This is being engineered to repair and/or replace damaged or diseased human tissues, and directly has a bearing on developing safer and more effective healthcare treatments. It also opens up the opportunity for cost effective patient specific tissue engineering to evolve. However, fundamental obstacles include balancing scaffold properties to; optimise resolution, cell migration, proliferation and differentiation need to be overcome, one step at a time. By further engineering this process then we can produce tissues which have measurable mechanical, metabolic and functional properties. This is from the perspective of using shaped scaffold bioprinting technology, which produces a complex organ structure. The potential to produce functional tissues on demand, made in a controlled and safe way for use in humans could one day revolutionise the future of healthcare.

DOI: 10.1530/endoabs.50.APW1.3

Early Career Prize Lectures

ECP1.1

Insights into G-protein coupled receptor (GPCR) trafficking and biased signalling by studies of calcium homeostasis

Caroline Gorvin
University of Oxford, Oxford, UK.

G-protein coupled receptors (GPCR) mediate the effects of multiple hormones, and consequently are fundamental for endocrine functions including glucose homeostasis, thyroid function, fertility, control of urine output, and bone remodelling. Mutations in genes encoding GPCRs result in endocrine disorders, and studies of these mutations has improved understanding of GPCR signalling and trafficking pathways, and could facilitate novel therapies. The calcium-sensing receptor (CaSR) is a class C GPCR that detects extracellular calcium concentrations, and modulates parathyroid hormone secretion and urinary calcium excretion to maintain calcium homeostasis. The CaSR utilises multiple G-proteins ($G\alpha_{q/11}$, $G\alpha_{i/o}$ and $G\alpha_{12/13}$) to mediate signalling effects including activation of intracellular calcium release and mitogen-activated protein kinase pathways, membrane ruffling, and inhibition of cAMP production. By studying loss- and gain-of-function mutations in CaSR, and proteins within its regulatory pathway, which cause familial hypocalciuric hypercalcaemia (FHH) and autosomal dominant hypocalcaemia (ADH), respectively, we have elucidated novel GPCR signalling and trafficking mechanisms. For example, by investigation of an ADH-associated CaSR-Arg680Gly mutation, we identified a structural motif that mediates biased signalling by activating a novel β-arrestin-mediated G-protein-independent mechanism that is not present in WT CaSR. In addition, analyses of FHH causing mutations in the adaptor protein 2 σ-subunit (AP2σ), a protein critical for clathrin-mediated endocytosis, have uncovered novel mechanisms by which CaSR is internalised, and demonstrated that CaSR can signal by a sustained endosomal pathway. Furthermore, we have shown that CaSR signalling from the cell surface uses multiple G-protein pathways, whilst sustained signalling is mediated only by the $G_{q/11}$ pathway. Thus, studies of FHH and ADH associated mutations have revealed novel steps by which CaSR mediates signalling and compartmental bias, providing a mechanistic basis for pluridimensional GPCR signalling.

DOI: 10.1530/endoabs.50.ECP1.1

ECP1.2

The role of hypoxia in the physiology and pathology of menstruation

Jacqueline Maybin[1], Alison Murray[1], Nikhil Hirani[1], Philippa Saunders[1], Peter Carmeliet[2] & Hilary Critchley[1]
[1]University of Edinburgh, Edinburgh, UK; [2]KU Leuven, Leuven, Belgium.

Heavy menstrual bleeding (HMB) is common and debilitating but it remains a taboo subject. Hence its cause remains undefined, resulting in non-specific hormone therapies with intolerable side effects.

Over 70 years ago it was proposed that progesterone withdrawal caused intense vasoconstriction and a transient endometrial hypoxia that resulted in menstruation. Subsequent research confirmed that inflammation initiated menses and disputed the role of hypoxia. By studying human tissue and a mouse model of 'simulated menstruation' we revealed that hypoxia is not necessary for endometrial breakdown but is essential for timely repair of the denuded endometrial surface to limit menstrual bleeding.

We found women with objectively measured HMB bled for two additional days versus those with normal bleeding, indicating defective endometrial repair. Hypoxia inducible factor (HIF-1) is the master regulator of the cellular response to hypoxia. Women with HMB displayed significantly reductioned endometrial HIF-1α and its downstream targets during menstruation, consistent with defective hypoxia. Prevention of endometrial hypoxia at menses and pharmacological or genetic reduction of HIF-1α in our mouse model did not prevent bleeding but significantly delayed endometrial repair. Further, we demonstrated that PHD inhibitors (HIF-1α stabilisers) significantly improved endometrial repair in our non-hypoxic menstruation model, revealing a promising, non-hormonal therapeutic strategy for women with HMB.

DOI: 10.1530/endoabs.50.ECP1.2

Meet The Expert Sessions

Pitfalls of Testosterone Replacement in Ment

MTE1

Pitfalls of testosterone replacement in men: Too much of a good thing?

Channa Jayasena
Imperial College London, London, UK.

Testosterone plays a critical role in sexual function, muscle growth and bone mineralisation, and has important behavioural effects in men. Levels of circulating testosterone decline by approximately 1% annually from the age of 40 years onwards. However some of the symptoms of low testosterone are non-specific, and may be caused by co-morbidities rather than low testosterone itself. Safety concerns have been raised regarding risks of cardiovascular events and prostatic growth in men during testosterone therapy. There is also an increasing public awareness of age-related low testosterone in men, which is causing an increase in prescribing of testosterone replacement in primary care. Testosterone replacement is clearly beneficial when levels of testosterone are very low, and patients are young enough to have minimal exposure to any adverse effects. However, in older men, or men with co-morbidities or borderline levels of testosterone, the endocrinologists face difficult decisions and confusion about current evidence. This session use real cases to give practical tips on assessing patients with low testosterone and selecting patients for testosterone replacement. It will also provide a concise update on the evidence and clinical guidelines in this core but controversial aspect of endocrine practice.

DOI: 10.1530/endoabs.50.MTE1

Metabolomics and Diet

MTE2

Modernazing dietary assessment by use of metabolic profiling

Isabel Garcia-Perez, Joram M Posma, Rachel Gibson, Edward S Chambers, Elaine Holmes & Gary Frost
Imperial College London, London, UK.

A major limitation of nutritional science is the objective assessment of dietary intake in free-living populations. Monitoring individuals' response to policy recommendations is based on self-reported dietary assessment tools, which are known to have high misreporting rates estimated at 30–88%. We have developed a novel analytical pipeline capable to classify people into consumers of a healthy or unhealthy diet based on urinary metabolic patterns, without relying on recorded food intake.

Here we aim to apply this methodology based on metabolic profiling to objectively monitor adherence to diet guidelines for free living people over time.

Methods

We conducted a randomised controlled clinical trial. 19 volunteers attended to a clinical research unit to follow four-dietary intervention representing 25, 50, 75 and 100% of adherence to WHO-healthy eating recommendations to increase fruits, vegetables, carbohydrates, dietary fibre and to decrease total fats, sugars, and salt, etc. A cohort of 20 volunteers collected spot urine samples once a week for 6 months and a matching 24-h food diaries for each day of the sample collection. Metabolic profiles were measured by ^{1}H-NMR spectroscopy.

Results

Analysis of ^{1}H-NMR spectroscopy data indicated significant differences in the urinary metabolic profiles of the four diets. These were used to predict the healthiness of the dietary habits of free-living people and tracking adherence to healthy eating recommendations over time.

Conclusions

This study demonstrates that a urinary metabolic profile developed in a highly controlled environment, independent of recorded food intake, can classify people into consumers of a healthy or unhealthy diet based on urinary metabolic patterns. This can be used for the objective monitoring of adherence over time to healthful diets in a population setting.

DOI: 10.1530/endoabs.50.MTE2

Autonomous Cortisol Secretion

MTE3

Autonomous cortisol secretion

Warrick Inder[1,2]
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The concept of subclinical hypercortisolism remains controversial in Endocrinology. Preclinical Cushing's syndrome, subclinical Cushing's syndrome or subclinical hypercortisolism, recently renamed in the European Society of Endocrinology Adrenal Incidentaloma Guidelines as 'autonomous cortisol secretion', is an example where a definition and name has not been universally agreed upon. Previous studies from Italy have used multiple tests of the hypothalamic-pituitary-adrenal (HPA) axis in patients with adrenal incidentaloma, and defined subclinical Cushing's as patients having any two abnormal tests. Earlier in 2017, a Korean group proposed modified criteria for subclinical hypercortisolism based on their study that identified which tests were most likely to predict (1) post-operative adrenal suppression and (2) presence of metabolic complications. The most sensitive combination of tests in this study was a cortisol of >138 nmol/l after 1 mg of dexamethasone OR post-dexamethasone cortisol >61 nmol/l, plus either ACTH <2.2 pmol/l *or* dehydroepiandrosterone-sulphate (DHEA-S) of <2.17 μmol/l in men and <0.95 μmol/l in women. Unlike subclinical hyperthyroidism, where TSH is able to be accurately quantitated, the ACTH immunoassay is not as robust at low concentrations. The addition of DHEA-S to the model provides another marker of cortisol autonomy in cases where ACTH is not fully suppressed. Several studies have shown that subclinical autonomous hypercortisolism is associated with several major comorbidities such as obesity, type 2 diabetes, hypertension and cardiovascular events, as well as osteoporosis and vertebral fractures. Adrenal incidentaloma patients with an abnormal 1 mg dexamethasone suppression test have increased mortality. Surgical resection may improve some of the comorbidities, but to date there has not been a study which has examined any beneficial effect on mortality. A multicentre randomised controlled trial is required to answer this important question.

DOI: 10.1530/endoabs.50.MTE3

The Time is Right

MTE4

Controlling for diurnal variation

David Ray
University of Manchester, Manchester, UK.

We all live in an oscillating environment driven by the Earth's rotation. This imposes predictable patterns of light and dark, to which almost all of life responds. There is a survival advantage in anticipating such environmental change, which has led to evolution of the autonomous circadian clock.

The circadian clock controls up to 40% of biochemical pathways, often acting to control a rate-limiting enzymatic step. Therefore, design and interpretation of biological experiments and clinical practice require acknowledgement of the power of the underlying circadian clock.

At the simplest level recording the time at which experiments are performed in relation to external cues, such as lights on (zeitgeber time; ZT), or clock time is important, to allow readers to assess and compare data. Amid concern about experimental reproducibility in biomedical research such recording should be mandated.

The core circadian clock in vertebrates is entrained by neural input from the retina to the light-dark cycle. However, the core clock is robustly buffered, and can only shift incrementally in response to changes in light-dark timing, such delayed transitions results in jet-lag. Typically two weeks acclimatization to a new light-dark schedule ensures full entrainment.

In addition, food availability is a powerful timing signal, and restricted feeding paradigms can be used to shift the liver metabolic clock to run out of phase with the central clock, e.g. by feeding nocturnal mice only during the day. Human studies can also be impacted by circadian factors, with major time of day variation in glucose tolerance, inflammation, and fat metabolism

to name a few. Developments in biomarkers, and drug trials both require consideration of circadian machinery to reduce noise, and to maximize therapeutic index respectively.

DOI: 10.1530/endoabs.50.MTE4

Opiate Induced Endocrinopathy
MTE5

Opioid-induced Endocrinopathy: 'Endocrinopathy of Trainspotting'

Fraser Gibb
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Use of long-term opioid analgesia has increased significantly in the past decade and dependency on prescribed opioids has been described as a 'public health emergency' in the United States. Opioid analgesia may be associated with excess mortality when compared to other classes of analgesia used in chronic pain. Opioids exert a range of effects across the hypothalamic-pituitary axes, which are potentially dependent on the chronicity of exposure. The largest body of evidence relates to effects upon reproductive hormones, which are mediated through inhibition of hypothalamic GnRH release and, consequently, LH and sex steroids. Hypogonadism may be present in up to 75% of male and 21% of female chronic pain patients treated with opioids. Whilst opioids can alter prolactin, thyrotropin and growth hormone secretion, it is much less clear whether this results in any clinically meaningful sequelae. Several case reports have identified opioids as a cause of secondary adrenal insufficiency. Recently, a small cross-sectional study of opioid-treated chronic pain patients identified adrenal insufficiency in 10% of patients receiving high dose opioids. However, chronic pain is also associated with perturbations in the HPA axis and further work is required to elucidate the effects (and potential mechanisms) of opioids on glucocorticoid production.

DOI: 10.1530/endoabs.50.MTE5

What Can Next Generation Sequencing do for You
MTE6

Abstract unavailable.

Growth Hormone Replacement Across the Ages
MTE7

Abstract unavailable.

Highlighting Management of Hyperthyroidism in Pregnancy
MTE8

Highlighting management of hyperthyroidism in pregnancy

Kristien Boelaert
University of Birmingham, Birmingham, UK.

Changes in thyroid hormone concentrations that are characteristic of hyperthyroidism must be distinguished from physiological changes in thyroid hormone economy that occur in pregnancy, especially in the first trimester. Gestational transient thyrotoxicosis, caused by very high serum hCG concentrations, is typically seen in women with hyperemesis gravidarum and occurs in one to two per 1000 pregnancies. This is generally a self-limiting condition which does not require antithyroid treatment and it is important to differentiate this from other forms of hyperthyroidism which may be associated with adverse pregnancy outcomes if untreated. In women of child-bearing age, Graves' disease (autoimmune hyperthyroidism) is the most common, although any type of hyperthyroidism including toxic nodular disease may occur during pregnancy. Since autoimmune disorders like Graves' disease usually improve during pregnancy it is rare for this condition to present for the first time during gestation. Importantly post-partum thyroiditis occurs in 5–10% of women and up to 50% of those affected ultimately develop permanent hypothyroidism. The differential diagnosis between transient thyrotoxicosis of pregnancy and Graves' disease can often be made on clinical grounds and the measurement of serum fT3 concentrations and TSH-receptor stimulating antibodies are useful diagnostic tools. Antithyroid drug treatment of hyperthyroidism in pregnant women is controversial because the usual drug – carbimazole – is occasionally teratogenic; and the alternative – propylthiouracil – can be hepatotoxic. Fetal hyperthyroidism caused by transplacental passage of TSH-stimulating antibodies can be life-threatening, and needs to be recognised as soon as possible so that treatment of the fetus with antithyroid drugs via the mother can be initiated. This Expert session will provide an overview of the clinical presentation, diagnosis and management of hyperthyroidism in pregnancy through case-based discussion.

DOI: 10.1530/endoabs.50.MTE8

Skills

Skills 1: How to engage with the media

SK1.1

Should we engage with the media?

Giles Yeo
University of Cambridge, Cambridge, UK.

Why do so many people believe what clearly are, at least to us in academia, 'alterative facts'? Ignorance and stupidity are answers that slip easily of the lips. If they only understood the science…why don't they look at the evidence? However, it is easy to forget that while we are all experts in our own little patch of intellectual or technical real-estate, we all have 'faith' and believe in a multitude of things that we understand little about every single day. How many of us truly understand how the brakes in our car work, or what keeps planes in the air? Are you qualified to assess the primary climate change data? Yet we all drive, or fly, and (most of us anyway) believe that humans have and continue to play a major role in global warming. We trust that other experts are doing their job and getting things right, and as a result society functions. The problem is, how does one tell an actual expert from a fake in this 'post-truth' era? If you are a 'doctor' claiming that vaccines cause autism, surely you know what you are talking about? The only way to combat this degradation of the value of truth, is to be, as academics, passionate about the truth. I will argue that engaging the media should be part of our arsenal to tell the truth and call out untruths wherever possible. I will discuss how to avoid the inevitable pit-falls, and how best to get your message across accurately, effectively and succinctly.

DOI: 10.1530/endoabs.50.SK1.1

SK1.2

Science versus the media

Jane Dreaper
BBC, London, UK.

Jane Dreaper is a long-standing BBC health correspondent, reporting on medical research and the NHS for radio, TV and the BBC News website. In this session, she'll talk about how health journalists work - and what she needs for her audiences when she interviews scientists or asks them for information and background.

DOI: 10.1530/endoabs.50.SK1.2

SK1.3

How to react to the media

Helen Simpson
UCLH, London, UK.

During this session I will discuss some ways of approaching requests for interviews by the media. The media can be main stream media such a television or radio, social media such as Twitter or web based journals. It can be daunting to consider having your views for all to see or hear, however there are many reasons to engage with the media. I will discuss some strategies on how to react to requests for information and offer some suggestions on how to approach interviews and media requests for information.

DOI: 10.1530/endoabs.50.SK1.3

Futures

Futures 1: Your Future in Endocrinology and Diabetes

FUT1.1

Abstract unavailable.

FUT1.2

Why diabetes?

Munachiso Nwokolo
King's College London, London, UK.

As a physician, diabetes is a condition that you will inevitably encounter in your career. Over 4 million have been diagnosed with diabetes here in the U.K., and importantly this figure does not account for the thousands of symptomless individuals in whom diabetes has not yet been diagnosed. For scientists, diabetes is fascinating on a genetic, molecular and environmental level; glycaemic dysfunction affects every organ in the body. Decades of research have revealed multiple types of diabetes and effective treatments but there are many significant questions left to answer such as, *'what is the best way to manage type 1 diabetes?'* and *'is type 2 diabetes actually a heterogeneous group of different metabolic disorders?'*. My research focuses on the former question, particularly in a subset of the type 1 population who are at a greater risk of hypoglycaemia, individuals with impaired awareness of hypoglycaemia (IAH). IAH affects 1 in 4 people with long duration type 1 diabetes and increases the risk of severe and possibly life-threating hypoglycaemia 3–6 fold. We continue to investigate the aetiology, progression and therapeutic options for this group, my current research indicates the brain and behaviour are key factors. Pursuing diabetes as a career opens the door for you to ask a million questions, and meet great minds whilst pursuing the answers. Whether you are lab, technology or clinically focussed, this speciality encompasses robust and novel research, innovative technology and cutting-edge surgery. Diabetes, why not?

DOI: 10.1530/endoabs.50.FUT1.2

FUT1.3

Clinical academic opportunities in endocrinology

Louise Hunter
University of Manchester, Manchester, UK.

A clinical career in Endocrinology is full of research opportunities, be they in basic science, patient cohorts, or at the population level. Research enriches clinical practice, offers new skills, and presents new challenges. Here, partly based on my own experiences as a current Clinical Research Training Fellow, I discuss how to make the most of these opportunities, UK clinical academic training routes, funding options, and where to go for further support and advice.

DOI: 10.1530/endoabs.50.FUT1.3

Futures 2: Consultant Careers – Escape Options

FUT2.1

Medical management: the good, the bad and the ugly

Colin Johnston
West Herts Hospitals Trust, St Albans, UK.

This will be a personal reflection by an 'experienced' clinician who has spent much his consultant career in clinical management including 4 years as Medical Director of a large Acute Trust. I will try and highlight the advantages and benefits of being involved in clinical management for you the Clinician, the Trust and your Patients. I will also outline some of the problems and pitfalls that can arise but I will focus on how this career choice can be developed and be rewarding.

DOI: 10.1530/endoabs.50.FUT2.1

FUT2.2

How to make a success of private practice

Paul Belchetz
Nuffield Hospital, Leeds, UK.

Private Practice is not for everyone, but can complement and enhance one's professional life - even if one has a fairly limited involvement, hence not particularly large income. I can only speak from my personal experience. When I began I benefited from valuable advice from a senior colleague on how to inform GPs in one's locality, how to set fees at appropriate levels and when and how much increases can be made. It is vital to have an efficient secretary to ensure letters and billing is done accurately and promptly. In addition I have always maintained an accurate ledger, in order to deal with ensuring payment of bills owed and owing including tax. A good secretary is invaluable in chasing bad debts effectively but properly. At the beginning I was asked to speak to local GPs on a variety of topics I was interested in, which in the case of Endocrinology is virtually all clinical areas as this is a discipline they often feel quite insecure about. A factor which I believe is likely to grow in providing satisfaction is the frequency that one establishes long standing relationships with complicated patients, seeing the evolution of their condition, when the pressure in NHS practice is for early discharge back to the GP – predisposing to delayed re-referral when problems arise. Offhand I can think of cases I have followed for 30 years or more, some providing novel clinical insights as a result.

A final issue is the necessity to provide ready access to oneself in case of urgent need, cover when one is away at meetings abroad or on holiday, and in my case, having relinquished licence to practice, ensuring appropriate handover to a suitable colleague if one cannot comfortably simply discharge back to the GP.

DOI: 10.1530/endoabs.50.FUT2.2

FUT2.3

Medico-legal practice: what, why and how?

James Ahlquist
Southend Hospital, Westcliff on Sea, UK.

Lawyers need doctors. When the work of the legal profession leads into areas of clinical medicine it is important that expert clinicians are there to explain and advise on the clinical issues. A good clinician can give valuable advice to the parties involved, and can also assist the courts in reaching a just and equitable conclusion.

In endocrinology an expert is most commonly asked to advise in matters relating to an allegation of clinical negligence. Sometimes we are asked about breach of duty: 'was the care provided of a reasonable standard?' More commonly we are asked about causation: for example, 'if a more timely referral had been made by the GP, would it have made a significant difference to the outcome?' An expert may also be asked to assist in the Coroner's Court, and occasionally in the Criminal Court. The clinical issues which come up reflect the whole range of practice in endocrinology and diabetes. An expert may choose to limit their involvement to certain topics where they have a particular expertise in their clinical work.

Working on clinical matters with high calibre lawyers can be challenging and stimulating. The clinical expert also has an opportunity to compare their own practice with that of other clinicians, and to have their opinions considered and scrutinised by their colleagues. Many find this a valuable educational experience and a unique form of peer review.

The demand for clinicians to be involved in legal work is increasing. In this session we will look at what is actually involved in medico-legal practice, and also the professional rewards and fulfilment that the work can bring.

DOI: 10.1530/endoabs.50.FUT2.3

Master Class

Masterclass 1: Bone Masterclass

MC1.1

Osteoporosis management: the cutting edge

Bo Abrahamsen
University of Southern Denmark, Odense, Denmark.

We all encounter patients with osteoporosis in our daily practice - indeed the risk of osteoporotic fractures is increased in most endocrine disorders. The basic principles of diagnosing and treating osteoporosis and eliminating secondary causes remain simple and we should master them. However, providing truly excellent osteoporosis management is challenging and is much more than using the latest osteoporosis medication.
There are challenges. Few clinicians have easy access to gold standard invasive procedures such as transiliac bone biopsies. Others may lack later generation DXA with VFA, TBS, HSA or AFF screening modes or bone turnover markers. Risk stratification of patients can be done using FRAX(TM) or by other algorithms such as Garvan score or Q-fracture. New anabolic agents are in the immediate pipeline but the range of existing drugs we can prescribe and/or have patients reimbursed for differs between countries and between health services within the same country. The majority of our patients have one or more conditions that would have precluded them from participating in the RCTs that led to licensing of the drugs we have available. CKD is a particular challenge. Drug development in osteoporosis is slow as secondary endpoints such as BMD and bone turnover are not recognized in the way that lipids or HbA1c are in drug development in other areas. Osteoporosis trials are therefore large and long and new drugs arrive only slowly.
To provide a cutting edge osteoporosis service we should be able to accurately classify patients as high or low risk using evidence based tools, identify secondary causes, provide clear guidance to patients about their disease and treatment, be able to select, prescribe and monitor the most appropriate interventions in terms of effect and safety and make decisions together with the patients about when to begin, pause or re-start treatment.

DOI: 10.1530/endoabs.50.MC1.1

MC1.2

A comprehensive secondary fracture prevention strategy

Muhammad Javaid
University of Oxford, Oxford, UK.

With over 500,000 fragility fractures a year and an ageing demographic, tackling the burden of osteoporosis is an urgent national priority. Effective secondary fracture prevention within the NHS could prevent over 20,000 fragility fractures including 9,000 hip fractures within 5 years. Ensuring this care gap is closed requires support from political prioritisation, business case models, getting started and getting improved and sustainable. This presentation will highlight the current models within the NHS, alignment with international standards and future plans to support your centre achieving a sustainable FLS.

DOI: 10.1530/endoabs.50.MC1.2

Masterclass 2: Delivery of Specialist Endocrine Care

MC2.1

Neuroendocrine tumours and the set up in the UK

John Newell-Price
University of Sheffield, Sheffield, UK.

Patients with neuroendocrine tumours require co-ordinated multidisciplinary and multimodal management, with appropriate referral pathways and access to timely expert care. This is exemplified by the European Neuroendocrine Tumour Society (ENETS) Centres of Excellence (CoE). There are forty CoE in Europe, ten of which are in the UK. The bar to achieve CoE status is set high, and the standards used for the audit assessments are appropriate to deliver best care even where centre status has not been sort or achieved. The UK and Ireland Neuroendocrine Tumour Society (UKINETS) and NET patient Foundation work closely with centres and aim to drive up standards across the UK. Overall, the UK is well-served by the existing CoE centres and other centres, and the collaborative model of regional hubs with local spokes providing excellent care and pathways in many regions. Such a model has been proposed by the CRGs for Specialised Endocrinology and Specialised Hepatobilary Disease as an optimum template for NHSE commissioning, and can serve as a template for specialised services in general.

DOI: 10.1530/endoabs.50.MC2.1

MC2.2

Abstract unavailable.

MC2.3

Abstract unavailable.

MC2.4

Abstract unavailable.

Debate

This House Believes that the UK Population Trend in Obesity Cannot be Reversed Without Food Taxation

D1.1

Debate: this house believes that the UK population trend in obesity cannot be reversed without food taxation

Roy Taylor
Newcastle University, Newcastle upon Tyne, UK.

The epidemic nature of obesity/overweight throughout the developed and less-developed world suggests that major new influences are at play. Correct identification of these influences must precede discussion of what action can rationally be planned. The widespread failure to recognise that this problem concerns the whole population and not merely those with a BMI over the arbitrary normal level is a critical factor in appreciating the nature of the problem. The lack of efficacy of exhortations to lose weight, and the potential effect of specific targets for food taxation, such as a sugar tax, will be considered.

DOI: 10.1530/endoabs.50.D1.1

D1.2

Abstract unavailable.

Nurse Session

Nurse Session 1: Cushing's disease

N1.1

Abstract unavailable.

N1.2

Cushing's research – Hot topics

John Newell-Price
University of Sheffield, Sheffield, UK.

Recent years have seen major advances in our understanding of the causes of adrenal and pituitary Cushing's syndrome. Careful molecular analyses have yielded new information about the underlying cellular mechanisms leading to the excess secretion of ACTH from the pituitary or cortisol from the adrenal. Unpicking these mechanisms has allowed proposals for new clinical trials of medical treatments for Cushing's disease. Intriguingly, inherited germ line mutations appear to account for some uncommon forms of bilateral adrenal disease, and this has implications for family screening of potentially affected relatives.

Diagnostic strategies are evolving and the most recent data suggest that salivary cortisone rather than salivary cortisol best reflects serum cortisol, and it is being assessed in states of cortisol excess. It is likely to be a sensitive and accurate means for diagnosis and monitoring.

A large-scale global clinical trial has demonstrated the efficacy of monthly pasireotide for Cushing's disease, a treatment which is already approved as an s.c formulation by NHSE for the treatment of Cushing's disease under certain constraints. Another global trial is now fully recruited assessing olidrostat, a new steroidogenesis inhibitor. Other novel approaches include assessment of levo-ketoconazole, antisense to the glucocorticoid receptor and antibodies designed to prevent the action of ACTH.

Careful quality of life assessments and disease-specific questionnaires have allowed demonstration of the devastating impact that Cushing's can have, even after remission of active disease.

Together, these are exciting times for Cushing's research, which should translate into better care for patient for patients within the next few years.

DOI: 10.1530/endoabs.50.N1.2

N1.3

Cushing's disease from a patient's perspective

Samantha Harbut
The Pituitary Foundation, Bristol, UK.

During this presentation I would like to share my Cushing's journey with you. Having found it difficult to achieve a diagnosis, despite a deterioration in my health, I was both relieved and terrified when I was finally told I had a pituitary tumour, which was driving the production of excess cortisol.

Whilst being extremely grateful for the specialist treatment I received, and my continual monitoring, I welcomed this opportunity to explain what a diagnosis such as this means for patients like myself. That tests, medication, surgery and scans are necessary is in no doubt, and undoubtedly saved my life, but my aim is to help medical professionals understand the true impact of such an illness, together with the upheaval and life changes that such a diagnosis brings.

However, rather than being a negative event, I choose to view my diagnosis as a positive experience, and hope to share that with Conference too.

DOI: 10.1530/endoabs.50.N1.3

Nurse Session 2: Diabetes Insipidus

N2.1

Clinical Presentation and Diagnosis of Cranial Diabetes Inspidus

Miles Levy
University Hospitals of Leicester, Leicester, UK.

Cranial Diabetes Insipidus is a potentially fatal disorder if not diagnosed and treated appropriately. The diagnosis can either be made in the outpatient setting, whereby the main differential diagnosis is Primary Polydipsia (PP), or during a hospital admission, where patients can be prfoondly unwell, dehydrated and hypernatraemic. In the ouptatient setting, it can sometimes be difficult to distinguish between DI and PP, but usually severe Cranial DI is clinically and biochemically obvious, characterised by extreme thirst and the pasing of high volumes of dilute urine. Cranial DI is usually associated with pituitary disease, although there are other causes which will be covered in the lecture. In the acute situation, there have been high profile cases in the media of potentially preventable deaths. As part of this talk, I will present the findings of a survey done on behalf of the Clinical Committee for the SFE, which higlights common areas of risk around the UK. The hope is that in this session, there will be an interactive discussion with the audience about how we can best educate health care professionals and the public to improve the recognition and understanding of this important condition.

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N2.2

Abstract unavailable.

N2.3

Challenging cases in DI

Stephen Ball[1,2]
[1]Central Manchester University Hospitals, Manchester, UK; [2]MAHSC, Manchester, UK.

Diabetes Insipidus (DI) results from a relative or absolute deficiency in either the production or action of the posterior pituitary hormone Vasopressin (AVP), the principle endocrine regulator of renal water excretion. The challenges in DI encompass its diagnosis, its treatment and in managing the co-morbidities and complications of the condition. This presentation will cover all these elements, highlighting cases that illustrate some of the key principles in the clinical approach to this important endocrine problem.

DOI: 10.1530/endoabs.50.N2.3

Senior Endocrinologists Session

SE1.1

Reproductive adaptability: Nature's cunning plan

Richard Sharpe
University of Edinburgh, Edinburgh, UK.

Reproduction is our biological reason for being. Evolution has shaped us via countless millennia with this one purpose in mind. Our development from an early embryo through to adulthood is geared to making us fit to reproduce, a process that is closely connected to nutrition and energy stores. Seasonal and other fluctuations in food supply has been a key evolutionary shaper of the reproductive process, as illustrated by seasonal breeding species. Humans have echoes of this seasonality and nutrition/energy stores have well-established relationships to puberty timing and fertility, at least in females. In view of the central importance of reproduction and the intimate relationship between nutrition and reproduction, it can be hypothesized that we have evolved mechanisms to enable adaptation to fluctuations in nutrition so as to better fit offspring to their perceived (nutritional) environment, and thus give them a reproductive advantage. This talk will argue that we already have evidence of this from 'fetal programming' studies and from 'inter-generational' effects following experimental manipulation of parental (especially paternal) diet and consequent metabolic changes in resulting offspring. It will be hypothesized that the epigenetic reprogramming of germ cells that occurs during three key life phases (fetal life, post-fertilisation, gametogenesis) provides the means for sensing of the perceived (nutritional) environment so as to induce adaptive epigenetic changes that ultimately alter offspring metabolic function. It will further be argued that an unbalanced, modern Western diet, which is deficient in 'epigenetically active' plant-derived factors (e.g. folate) may have resulted in changes to the epigenome of offspring that lead to adverse metabolic changes which predispose to 'modern Western diseases'. If these hypotheses are true, parental and even perhaps grandparental diet, could have consequences for health of future generations. How important this might be is unknown.

DOI: 10.1530/endoabs.50.SE1.1

SE1.2

Cancer Survivors-the New Endocrine Epidemic

Stephen Shalet
Christie Hospital, Manchester, UK.

One of the success stories of modern medicine is the high cure rate of common childhood cancers. After an early period of denial, the existence of longterm complications, predominantly treatment-related, is acknowledged. By 2010 one in 250 of the adult population was a longterm survivor of childhood cancer. In 2014 420,000 childhood cancer survivors were estimated in the USA alone. Subsequently Moustoufi-Moab *et al*. (2016) reviewed 14,000 survivors of childhood cancer, median age 6 years at cancer diagnosis and 32 years at last follow-up. 44% had at least one, 16.7% had at least two and 6.6% had three or more endocrinopathies. The endocrinopathies include hypopituitarism, hypoadrenalism, hyperthyroidism, hypothyroidism, thyroid tumours, hyperparathyroidism, obesity, infertility, hypogonadism, osteoporosis, metabolic syndrome, insulin resistance, diabetes mellitus. At the same time but more slowly, increasing numbers of survivors of adulthood cancers are presenting with endocrine sequelae, such that 62% of those irradiated for nasopharyngeal cancer are hypopopit 5 years later and 13.6% of chemotherapy-treated men with testicular tumours,for whom survival rates are 95%, are frankly hypogonadal. New treatments, such as proton beam irradiation and immune checkpoint inhibitors have been introduced but endocrinopathies remain an issue. The endocrine care of these survivors has major implications in terms of staff and time. Treatment exists however for most of these endocrinopathies. Therefore there is an obligation for Endocrinologists to deliver a service.

DOI: 10.1530/endoabs.50.SE1.2

SE1.3

The mystery of puberty – why it has been such a tough nut to crack?

Tony Plant
University of Pittsburgh, Pittsburgh, Pennsylvania, USA.

Puberty is a major event in human development that impacts the individual, the family and society in general, but with exception of its endocrinology the fundamental biology underlying the process is poorly understood. Puberty is the result of the complete activation of the pituitary-gonadal axis that, in man, is triggered by re-augmentation of pulsatile hypothalamic GnRH release after approximately a decade of pre-pubertal development during which time this mode of neuropeptide secretion is held in check by a gonad-independent neurobiological brake. Fundamental understanding of the neuronal basis of GnRH pulse generation has advanced dramatically since the discovery in 2003 of the importance of hypothalamic kisspeptin signaling to the reproductive axis: indeed compelling evidence is beginning to emerge that indicates kisspeptin release (at the level of the GnRH nerve terminals in the median eminence) from neurons located in the arcuate/infundibular nucleus provides the output of the pulse generator. The mechanisms that restrain the GnRH pulse generator from infancy until puberty and therefore suppress the pulsatile kisspeptin drive to the GnRH neuronal network, and the physiological control system that times, first, the application during infancy and, then, removal of this restraint at the end of juvenile development remain a mystery. While insight is being provided by molecular genetics of human disorders (e.g. makorin ring finger protein full 3), animal models for pursuing such leads are limited. Species such as the mouse, which are genetically tractable, do not exhibit a puberty that is delayed by a robust "primate like" neurobiological brake. Although the monkey provides a more suitable model for the human situation, studies of non-human primates are costly and difficult to execute; a situation that is exacerbated by the strengthening socio-political climate that views animal research, and particularly that on primates, negatively.

DOI: 10.1530/endoabs.50.SE1.3

SE1.4

You think you understand ACTH and Cushing's syndrome?

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The majority of patients with Cushing's syndrome are ACTH-dependent, but the diagnosis of ACTH-dependence, and then the differential diagnosis between Cushing's disease and the ectopic ACTH syndrome, is dependent on the measurement of ACTH. In the mammalian adult anterior pituitary, POMC is cleaved into a variety of products including the 'normal' ACTH(1-39). In the pars intermedia (present in the human fetus and most mammals), ACTH is cleaved further by the prohormone converting enzyme, PC2, to ACTH 1-17 and ACTH 18-39 (CLIP): ACTH 1-17 (which still has significant ACTH receptor activity) is then processed at its C-terminal to ACTH 1-13 amide (α-MSH). This type of processing of ACTH can occur in ectopic tumours and some pituitary adenomas. These fragments generally do not give signals in ACTH two-site immunoassays, but if they are secreted many-fold in excess to ACTH they will bind to and swamp the individual antibodies without forming the two-site liaison that is necessary for the detection of any intact ACTH present. In addition, patients with aggressive ectopic ACTH secreting tumours, especially small cell lung tumours, often secrete high levels of the ACTH precursors. While it is possible to assess the concentrations of ACTH precursors using a specific two-site ACTH precursor assay, most ACTH assays only detect about 2% of ACTH precursors which may confuse the diagnosis. Thus, plasma from patients with ectopic ACTH-producing tumours may often give erroneous signals in two-site immunoassays for ACTH. Such patients may even be thought to harbour adrenal tumours rather than being ACTH-dependent, and there may be discordance between the levels of ACTH and cortisol. Additionally, the very region of ACTH which is important for adrenal receptor activity, and the target of the initial trypsin-like proteolysis by PC2 in the pars intermedia, is also susceptible to cleavage by other trypsin-like enzymes. This means that the collection and storage of plasma for subsequent measurement of intact ACTH by two-site immunoassay can be a problem. Thus, other more stable and immunogenic co-secreted parts of POMC such as pro-γ-MSH (which can cause gross adrenal hypertrophy and hyperplasia), the joining peptide or lipotrophin, or ACTH precursors might thus be more reliable markers for the diagnosis and differential diagnosis of Cushing's syndrome.

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Oral Communications

Early Career Oral Communications

OC1.1

Neurokinin 3 receptor antagonism is a highly effective, novel treatment for menopausal hot flushes with rapid onset: a phase 2, randomised, double-blind, placebo-controlled trial

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Background
Hot flushes (HF) affect 70% of menopausal women and can be debilitating. Oestrogen administration is effective but not without risk. Neurokinin B signalling is increased in menopausal women, and is likely critical in the aetiology of their HF. We therefore hypothesised that a neurokinin 3 receptor (NK3R) antagonist could attenuate menopausal flushing.
Design
This single-centre, phase 2, randomised, double-blind, placebo-controlled, crossover trial assessed the efficacy of an oral NK3R antagonist (MLE4901) on menopausal HF (Clinicaltrials.gov NCT02668185; funding MRC, NIHR). Of 68 women screened, 37 were randomised and included in an ITT analysis (aged 49–62 years, with >7 HF/24 h some of which were bothersome or severe). Participants received 4 weeks of MLE4901 and four weeks of placebo in random order separated by a 2 week washout period. Primary outcome was total number of HF during the fourth week of both treatment periods. *Post-hoc* time course analysis was conducted in a modified ITT population (minimum $n=34$) to ascertain the therapeutic profile of MLE4901.
Results
Primary outcome: MLE4901 significantly reduced the total weekly number of HF by 45% points compared to placebo (adjusted means: placebo 49.01 (CI: 40.81–58.56), MLE4901 19.35 (CI: 15.99–23.42), $P<0.0001$), and by 73% compared to baseline. By day 3 of treatment, MLE4901 reduced the frequency of HF by 72% compared to baseline (CI: −81.3 to −63.3, $P<0.0001$; 51% point decrease compared to placebo (CI: −63.5 to −38.4)), and this effect persisted throughout dosing. HF severity was also reduced by 38% compared to baseline by day 3 (CI: −46.1 to −29.1, $P<0.001$), as was HF bother by 39% (CI: −47.5 to −30.1, $P<0.0001$), and HF interference by 61% (CI: −79.1 to −43, $P=0.0006$); all continued to improve throughout dosing and were positively correlated ($r=0.76$–0.93, $P<0.001$). Treatment was well tolerated.
Conclusion
NK3R antagonist therapy (MLE4901) could be practice changing as it is well tolerated, and HF symptoms are rapidly relieved without oestrogen exposure. Larger scale studies of longer duration are imminent.

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OC1.2

Co-administration of 5α-reductase inhibitors worsens the adverse metabolic effects of prescribed glucocorticoids

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Glucocorticoids (GC) are commonly prescribed and their use is associated with adverse metabolic side effects. 5a-reductase (5aR) inhibitors are also frequently prescribed mainly for their ability to inhibit the conversion of testosterone to dihydrotestosterone. However, they also have a role to inactivate and clear GCs. We hypothesised that 5aR inhibitors have the potential to exacerbate the adverse metabolic effects of GCs. We conducted a prospective, randomised, study in 19 healthy male volunteers (age; 45±8.5 years, BMI; 27.1±3.1 kg/m^2). Participants underwent metabolic assessments including a 2-step hyperinsulinaemic, euglycaemic clamp incorporating stable isotopes, adipose tissue microdialysis and biopsy. They were then randomised to receive either prednisolone (10 mg daily) or prednisolone (10 mg daily) and a 5aR inhibitor (finasteride 5 mg daily or dutasteride 0.5 mg daily) for 7 days; metabolic assessments were then repeated. We have previously shown that high dose GC administration decreases glucose utilization and that 5aR inhibitors alone are without effect. In this study, prednisolone alone did not alter glucose utilization (M-value; 3.2±1.3 *vs* 2.8±1.6 mg/kg per min, $P=0.37$), but was significantly decreased by co-administration with a 5aR inhibitor (4.0±2.0 *vs* 2.6±1.3 mg/kg per min, $P=0.02$). Similarly, prednisolone did not impair the ability of insulin to suppress circulating non-esterified fatty acids (NEFA) (0.15±0.27 *vs* 0.13±0.13, $P=0.88$), unless co-administered with a 5aR inhibitor (0.15±0.1 *vs* 0.29±0.18, $P=0.01$). In addition, 5aR inhibition enhanced the ability of prednisolone to antagonize insulin-mediated suppression of lipolysis as measured by glycerol release into adipose tissue interstitial fluid (−198±133 *vs.* −69±85 μmol/l, $P=0.04$). Finally, 5aR inhibitors augmented the ability of prednisolone to induce lipogenic gene expression within subcutaneous adipose tissue (FASN: Fold change=1.3, $P=0.04$). We have demonstrated that 5aR inhibitors exacerbate the adverse effects of prescribed GCs. This has significant translational implications, not only with regards to the need to consider steroid dose reductions, but also the necessity for increased vigilance for the development of adverse effects.

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AMEND Young Investigator Award

OC1.3

Antioxidant pathway targeting as a therapeutic approach in adrenocortical carcinoma

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Adrenocortical Carcinoma (ACC) is an aggressive malignancy with poor response to chemotherapy. Here we evaluated a potential new treatment target for ACC, focusing on the mitochondrial NADPH generator Nicotinamide Nucleotide Transhydrogenase (NNT). NNT has a central role within the mitochondrial antioxidant pathways, protecting cells from oxidative stress. Inactivating NNT mutations lead to isolated primary adrenal insufficiency, suggesting a selective vulnerability of adrenocortical cells to NNT loss. A TCGA database search confirmed increased NNT expression in ACC. Therefore, we hypothesised NNT silencing in ACC cells will induce toxic levels of oxidative stress. To explore this, we transiently knocked down NNT in NCI-H295R ACC cells by siRNA transfection. NNT silencing increased intracellular levels of oxidative stress; this resulted in a dramatic suppression of cell proliferation and higher apoptotic rates, as well as sensitising cells to chemically-induced oxidative stress. Steroidogenesis was paradoxically stimulated by NNT loss, as demonstrated by comprehensive steroid profiling. Next, we generated a stable NNT knockdown model in the same cell line (lentiviral shRNA transfection), to understand the chronic effects of NNT silencing. After culture for 1–3 months, cells adapted metabolically to stable NNT knockdown, restoring their redox balance and resilience to oxidative stress, although their proliferation remained suppressed. This was associated with higher rates of oxygen consumption. The molecular pathways underpinning the cellular response to transient and chronic NNT loss were explored in detail by RNA sequencing and whole-metabolome analysis. Transient NNT knockdown led to changes in core pathways controlling cellular proliferation and viability. Stable (chronic) knockdown was characterised by changes consistent with accelerated protein turnover and up-regulation of antioxidant polyamines, which can facilitate partial adaptation to oxidative stress. Our study provides the first pre-clinical evidence of the therapeutic merit of antioxidant

targeting in ACC, as well as delineation of the long-term adaptive response of cells to oxidative stress.

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British Thyroid Association Award

OC1.4

An investigation into sodium-iodide symporter (NIS) dimerization and its impact on radioiodide uptake in thyroid cancer

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The ability of the thyroid to accumulate iodide via the sodium-iodide symporter (NIS) can be utilised to successfully treat the majority of thyroid cancers with radioiodide. However, approximately 25% of thyroid cancers lose this functional NIS activity and become unresponsive to radioiodide therapy, resulting in a poorer prognosis. Our knowledge of NIS regulation is limited, but as dimerisation of NIS has been proposed, we sought to investigate NIS dimerisation and its impact on radioiodide uptake. Dimerisation of wild-type NIS was confirmed using proximity ligation assays (PLA) in both a thyroid (SW1736) and non-thyroid (HeLa) cell line. To quantitatively assess NIS dimerisation using Förster resonance energy transfer (FRET), novel constructs conjugating NIS to one of the fluorescent proteins citrine (YFP) or cerulean (CFP) were created. YFP/CFP ratio of the NIS-fluorophore constructs increased compared to fluorophores alone (1.71 ± 0.10 vs 1.09 ± 0.16, $P < 0.05$ in SW1736 cells, $n = 3$ and 1.73 ± 0.10 vs 1.13 ± 0.04, $P < 0.01$ in HeLa cells, $n = 3$), further validating NIS dimerisation. To identify residues potentially involved in dimerisation, a homology model of NIS structure was built based on the dimeric crystal structure of the bacterial protein vSGLT using the modelling platform Phyre2. Using site-directed mutagenesis, we then mutated five residues identified from our homology model (D237A, Y242A, T243A, Q471A and A525F), and two putative dimerisation motifs identified in the literature (a glycine zipper motif in transmembrane domain (TMD) 12, with key glycine residues mutated to valine, and a leucine zipper motif in TMD6, with key leucine residues mutated to alanine). PLA suggested that all mutants still retained the ability to dimerise, indicating that dimerisation involves multiple, or as yet undiscovered, residues. In summary, NIS dimerisation has been conclusively demonstrated using two discreet methodologies. Further work is ongoing to determine the critical residues, cellular localisation and regulation of NIS dimerisation and its impact on radioiodide uptake.

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OC1.5

An essential physiological role for MCT8 in bone

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T3 is an important regulator of skeletal development and adult bone maintenance. Thyroid hormone action requires efficient transport of T4 and T3 into target cells. We hypothesized that monocarboxylate transporter-8, encoded by *Mct8* on the X-chromosome, is an essential thyroid hormone transporter in bone. To test this hypothesis, we determined the juvenile and adult skeletal phenotypes of male *Mct8* knockout mice (*Mct8KO*) and *Mct8D1D2KO* compound mutants, which also lack the ability to convert the prohormone T4 to the active hormone T3. *Mct8KO* mice have mild central resistance to thyroid hormone with decreased T4 concentrations and slightly elevated T3 concentrations. By contrast, *Mct8D1D2KO* mice have severe central resistance to thyroid hormone with systemic hyperthyroidism. Intrauterine skeletal development was normal in both *Mct8KO* and *Mct8D1D2KO* mice, whereas postnatal endochondral ossification and linear growth were delayed in both *Mct8KO* and *Mct8D1D2KO* mice ($P < 0.05$) and normalised by 12 weeks of age. This growth delay was accompanied by abnormal mineral content in *Mct8KO* and *Mct8D1D2KO* mice between 2 and 16 weeks of age ($P < 0.001$). Adult *Mct8KO* and *Mct8D1D2KO* mice had decreased bone mass and mineralisation but only compound mutants had reduced bone strength with decreased yield and maximum loads ($P < 0.05$). Bone resorption was increased in *Mct8D1D2KO* mice whereas bone formation parameters were not changed in either *Mct8KO* or *Mct8D1D2KO* mice. Delayed bone development and maturation in *Mct8KO* and *Mct8D1D2KO* mice is consistent with decreased thyroid hormone action in growth plate chondrocytes despite elevated serum T3 concentrations, whereas low bone mass and osteoporosis reflects increased thyroid hormone action in adult bone due to elevated systemic T3 levels. These studies demonstrate an essential role for the thyroid hormone transporter MCT8 in chondrocytes during skeletal development, and reveal the importance of other transporters in adult bone maintenance.

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OC1.6

Investigating the role of AIP in mouse pituitary adenoma formation

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Introduction

Mutations in the aryl hydrocarbon receptor-interacting protein (*AIP*) predispose humans to pituitary adenomas, mostly GH and sometimes prolactin-secreting adenomas. Rodent models of heterozygous *AIP* loss provided mixed results, with little phenotype in heterozygote global knockouts to 80% in somatotroph-specific homozygote knockout animals. However, human patients with an *AIP* mutation often have mixed GH-PRL adenomas and, in a smaller proportion, pure prolactinomas. Therefore, we have generated a transgenic model with pituitary-specific *AIP* knockout using an early transcription factor *Hesx1*.

Aim

To characterize a transgenic mouse model of early stage pituitary-specific deletion of *AIP*.

Methods

AIP was specifically inactivated in the anterior pituitary at the embryonic stage by crossing animals bearing floxed *AIP* alleles with mice expressing *Cre* recombinase under the *Hesx1* regulatory element. Tissue was collected for immunohistochemistry and size measurements. IGF1 blood levels were measured at regular intervals.

Results

AIP null mice are significantly larger compared to their littermate controls by the age of 3 months (23.9 ± 2.27 vs 28.5 ± 3.03 g, $P < 0.01$) with higher levels of IGF1 as early as 2 months (333.31 ± 35.70 vs 472.66 ± 86.81 ng/ml, $P < 0.005$). At 15 months, homozygote knockout mice had hypertrophic hearts (9.19 ± 0.43 vs 10.79 ± 1.02 mm, $P < 0.0001$) and the pituitary is enlarged (1097556 ± 220927 vs 2155418 ± 513251 μm^2, $P = 0.02$) exhibiting features of hyperplasia and areas of adenomas positive for GH and prolactin. These abnormalities were observed with 100% penetrance. Heterozygote mice overall are not significantly larger, although some animals have abnormal pituitaries, suggesting that penetrance, similar to humans, is incomplete.

Conclusions

Using a transgenic approach we have established a KO mouse model of early *AIP* deletion specifically in the pituitary. Complete loss of *AIP* results in increased

body size and higher circulating IGF1 levels early on eventually leading to hyperplasia and tumour formation. This model provides an invaluable tool to study AIP-related tumorigenic processes and possible therapeutic interventions.

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Clinical Highlights

OC2.1

Mild autonomous cortisol excess in adrenal incidentalomas – metabolic disease burden and urinary steroid metabolome in 1201 prospectively recruited patients

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Background
Adrenal incidentalomas (AI) are found in approximately 5% of the adult population. Most AIs are benign; however, small-scale studies have indicated that 20–50% of patients harbouring a benign AI show biochemical evidence of mild autonomous cortisol excess (MACE), previously termed subclinical Cushing's syndrome. MACE is differentiated into MACE-1 (serum cortisol after overnight suppression with 1 mg dexamethasone (1 mg-DST) 50–140 nmol/l) and MACE-2 (1 mg-DST serum cortisol $>$ 140 nmol/l). MACE patients do not show clinically overt signs of Cushing's, but previous series have suggested an increased risk of metabolic disease. However, large-scale data about the metabolic impact of MACE are lacking.
Methods
We included 1201 AI patients with benign adrenocortical adenoma and 1mg-DST results from the prospective multi-centre EURINE-ACT study. All patients underwent detailed clinical phenotyping and provided a 24 h urine sample. Results of mass spectrometry-based urinary steroid profiling were compared to 162 healthy controls and 56 patients with clinically overt adrenal Cushing's syndrome, using a linear regression model adjusting for sex and age.
Results
MACE was found in 48% of patients (MACE-1 37%, MACE-2 11%), while 52% had non-functioning (NF) AIs. MACE was more frequent in women (NF: 64%, MACE-1: 67%; MACE-2: 77%). MACE AIs had a larger tumour diameter (median 32 mm vs 22 mm in NF) and were more often bilateral (31% vs 17% in NF). Metabolic disease burden increased with severity of cortisol excess (hypertension: NF 64%, MACE-1 67%, MACE-2 71%; type 2 diabetes: NF 18%, MACE-1 21%, MACE-2 25%). Urinary steroid profiling revealed significantly lower androgen and androgen precursor excretion and increased cortisol metabolite excretion in both MACE and Cushing's; both groups also showed significantly decreased 5a-reductase activity (all $P<0.001$).
Conclusions
MACE is highly prevalent in AIs and carries an increased metabolic disease burden. The MACE steroid metabolome signature is highly similar to Cushing's, including reduced glucocorticoid inactivation via 5a-reductase.

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OC2.2

Combined immunosuppression & radiotherapy in thyroid eye disease (CIRTED) trial: A multi-centre, double-masked, factorial randomised controlled trial

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On behalf of the Combined immunosuppression & radiotherapy in thyroid eye disease (CIRTED) Investigators
Background
Thyroid eye disease is an inflammatory orbital condition which causes visual dysfunction and psychological morbidity. Current evidence is conflicting on the benefit of radiotherapy and antiproliferative immunosuppression *in addition* to systemic corticosteroid treatment. In particular, little is known about clinical outcomes more than 24 weeks after initiating these interventions.
Methods
CIRTED investigated the efficacy of orbital radiotherapy (RT) and azathioprine (AZA) vs placebo in combination with a standard 24-week tapering course of oral prednisolone in patients with active TED in a 2:2 factorial design. A composite outcome measure of treatment success was used with a primary end-point at 48 weeks.
Results
126 subjects were randomized and primary outcome data were available in 103 (82%). Sixty-six (52%) withdrew from their treatment allocation beyond the period of radiotherapy/sham-radiotherapy but before the primary end point (61% in AZA, 40% in RT). Withdrawal due to abnormal blood tests or side-effects was more frequent with AZA ($OR_{(adj)}$ =5.90 (95%CI 2.06, 16.9) $P=0.001$. In an intention-to-treat analysis, the adjusted odds ratio for improvement was 2.54 (95%CI 0.98, 6.60, $P=0.06$) for AZA and 0.93 (95%CI 0.38, 2.26) $P=0.87$ for RT. For those completing therapy improvement was more frequent on AZA ($OR_{(adj)}$ =7.01 (95%CI 1.70, 28.8) $P=0.007$) than RT ($OR_{(adj)}$ =1.49 (95%CI 0.45, 4.9) $P=0.50$).
Interpretation
In patients receiving a 24-week course of oral prednisolone, no additional treatment benefit was seen with RT. Completion rates of AZA treatment were low, however those completing treatment derived substantial benefit at 48 weeks.

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OC2.3

A novel IGSF1 mutation in a large Irish kindred highlights the need for systematic familial endocrine screening in the IGSF1 deficiency syndrome

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Background
Loss-of-function mutations in *IGSF1* result in X-linked congenital central hypothyroidism (CeCH), occurring in isolation or in association with additional pituitary hormone deficits. Intrafamilial penetrance is highly variable and a minority of heterozygous females are also affected. We identified and characterized a novel *IGSF1* mutation and investigated its associated phenotypes in a large Irish kindred.

Methods
A novel, hemizygous *IGSF1* mutation was identified by direct sequencing in two brothers with CeCH and its functional consequences were characterized *in vitro*. Genotype-phenotype correlations were investigated in the wider kindred.
Results
The mutant IGSF1 protein (c.2318T>C, p.L773P) exhibited decreased plasma membrane expression *in vitro* due to impaired trafficking from the endoplasmic reticulum. Ten hemizygous males, and 11 heterozygous females, exhibited characteristic endocrine deficits. Ireland operates a TSH-based CH screening programme, which does not detect CeCH; therefore genetic ascertainment preceded biochemical diagnosis of moderate CH in five of eight boys, and their 75 year-old grandfather. Tissue manifestations of hypothyroidism were variable; normal free T3 (FT3) levels and low/low normal reverse T3 (rT3) measurements suggested that preferential deiodination of FT4 to FT3 may help maintain tissue euthyroidism in some individuals. However, growth retardation, speech delay and obesity were associated with delayed diagnosis of endocrinopathy in five cases.
Conclusions
As observed with other loss-of-function IGSF1 mutations, L773P results in variably penetrant IGSF1 deficiency syndrome. Our observations emphasise the need for multi-generation genetic ascertainment in affected families, especially where TSH-based CH screening programmes may fail to detect CeCH at birth.

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OC2.4

Development of endocrinopathy following treatment of metastatic melanoma with an immune checkpoint inhibitor is associated with better response

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Background
Immune checkpoint inhibitors have revolutionized the treatment of metastatic melanoma, demonstrating durable responses, but can result in immune-related adverse events (irAEs). Endocrinopathies are amongst the more common adverse events, and thyroid dysfunction and hypophysitis being the most frequent; the latter of these has been positively correlated with oncological outcome. This study compared overall survival (OS), progression-free survival (PFS) and disease control rate in patients with and without endocrinopathy following treatment with ipilimumab, PD-1 inhibitors and combination treatment.
Patients and methods
The study was a retrospective review of 338 patients with metastatic melanoma treated with ipilimumab, nivolumab, pembrolizumab or combination of ipilimumab and nivolumab at the Royal Marsden Hospital between 1/1/2010 and 31/12/2016. Thyroid dysfunction was defined as any abnormal thyroid dysfunction following treatment (with the exception of secondary hypothyroidism without evidence of other pituitary involvement). Hypophysitis was defined as deficiency in more than one pituitary axes or deficiency in one pituitary axis plus enlargement of the pituitary gland on MRI. Follow up imaging results were evaluated to assess response to treatment and date of progression.
Results
Hypophysitis was diagnosed in 22 patients and thyroid dysfunction in 116 patients. OS was significantly prolonged in hypophysitis compared to no endocrinopathy patients (HR, 0.22; 95% CI, 0.10–0.46; $P<0.001$) and in patients with thyroid dysfunction compared to no endocrinopathy (HR, 0.49; 95% CI, 0.36–0.66; $P<0.001$). PFS following first-line treatment was also significantly higher in both hypophysitis and thyroid dysfunction groups compared to patients without endocrinopathy (respective HR, 0.42; 95% CI, 0.25–0.70; $P<0.001$ and HR, 0.71; 95% CI, 0.56–0.91; $P<0.001$), as was the disease control rate ($P\leq0.001$ and $P=0.01$ respectively).
Conclusions
The development of endocrinopathy in this cohort was associated with improved oncological outcome. We hypothesise that development of endocrinopathy in response to treatment with checkpoint inhibitors may be a marker of activation of the immune system and hence of the anti-tumour response.

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OC2.5

Additional value of 4D-CT in patients with primary hyperparathyroidism and negative conventional imaging; a reason to change primary imaging modality in patients over 60?

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Introduction
Minimally invasive surgical treatment of primary hyperparathyroidism (PHPT) requires optimal preoperative localisation imaging. Parathyroid four-dimensional CT (4D-CT) has been reported to provide greater sensitivity than MIBI-SPECT/CT in localizing parathyroid adenomas. We analysed the additional value of 4D-CT in our cohort of PHPT patients.
Materials and methods
Patients who attended our parathyroid clinic between February 2016 and April 2017, with biochemically unequivocal PHPT and meeting criteria for surgery were included. All patients underwent Ultrasound and MIBI-SPECT/CT. Patients with inconclusive imaging underwent additional 4D-CT.
Results
Fifty-two patients (77% female) with a mean age of 66.2 ± 14.9 years were included. To date 17/23 patients with inconclusive imaging results underwent additional 4D-CT. Surgical correlation so far has been positive in 4/4 positive 4D-CTs. An intrathyroidal parathyroid adenoma was found in 1 patient with a negative 4D-CT.
Conclusions and discussion
We have been able to radiologically localize a parathyroid adenoma in a majority of our PHPT patients with inconclusive imaging. Surgical correlation is ongoing, but results so far are promising. 4D-CT incurs radiation exposure, particularly to the thyroid and therefore should be used cautiously, especially in younger patients. Population risk for developing any cancer is 1/1000 after 4D-CT, 1/1700 after 4D-CT adjusted protocol and 1/2400 after MIBI-SPECT/CT. Lifetime attributable risk for thyroid cancer after 4D-CT is 1/100,000 in patients >60 years vs 1/2600 in patients of 30 years. MIBI-SPECT/CT is five times more expensive than 4D-CT (£630 vs £125). Currently, first line imaging consists of Ultrasound and MIBI-SPECT/CT. 4D-CT has additional value in PHPT patients with negative conventional imaging. We suggest that 4D-CT should be considered as first line imaging in patients over 60 years presenting with PHPT. Optimising the sensitivity of parathyroid imaging should result in more patients having minimally invasive surgery.

Table 1 Radiological localization parathyroid adenomas

	US	MIBI-SPECT/CT	4D-CT
Positive	29/52 (55.8%)	29/52 (55.8%)	13/17 (76.4%)
Negative	20/52 (38.5%)	22/52 (42.3%)	3/17 (17.6%)
Equivocal	3/52 (5.7%)	1/52 (1.9%)	1/17 (5.9%)

Table 2 Radiation exposure

	MIBI-SPECT/CT	4D-CT vs 4D-CT adjusted protocol	Annual UK Background Exposure
Calculated exposure	8.5 mSv	18 mSv vs 12 mSv	2.7 mSv

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OC2.6

Reduced early GLP-1 response in gestational diabetes is associated with hyperinsulinaemia and insulin resistance: a prospective case-control study

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Background
Glucagon-like peptide-1 (GLP-1) concentrations are reduced by 20–50% in type 2 diabetes but studies in women with gestational diabetes mellitus (GDM) are inconclusive. Our aim was to study the GLP-1 profile during a glucose tolerance test (GTT) at GDM diagnosis and its relationship with insulin levels.
Methods
A prospective study of selectively screened women was conducted. Plasma GLP-1, insulin and glucose were measured at 30-minute intervals during a 2-hour 75 g GTT. GDM was diagnosed according to UK NICE guidelines ($glucose_{0min} \geq 5.6$ mmol/l or $glucose_{120min} \geq 7.8$ mmol/l) and the parameters were additionally considered as continuous variables in linear regression models.
Results
Hundred and forty-five women were recruited and 19 developed GDM ($glucose_{120min}$ range 7.8–12.1 mmol/l). 19 controls, with the lowest $glucose_{120min}$ values in our cohort (range 4.0–4.5 mmol/l), were identified. GLP_{30min} concentrations were significantly lower in GDM women than controls after adjusting for covariates (Table 1). GLP-1 total area under the curve (AUC) was reduced by 13% in GDM (adjusted $P<0.05$) but mean GLP-1 and incremental AUC were similar. Serum insulin levels from 0 to 90 min were similar in the two groups but GDM women had over two times higher $insulin_{120min}$ (481 vs 211 pmol/l, adjusted $P=0.001$). GLP_{0min} and GLP_{30min} were negatively correlated with $insulin_{120min}$. GLP_{30min} also independently predicted insulin sensitivity index, measured by Stumvoll formula (β-coefficient = 0.152, $P=0.038$), thus contributing to post-prandial hyperglycaemia. There were no associations between GLP-1 levels at other time-points and any glucose or insulin parameters.
Conclusion
Total and early (GLP_{30min}) GLP-1 response are reduced by 13–20% in GDM women respectively. Lower GLP_{30min} levels are independently linked to lower insulin sensitivity, thus suggesting a novel mechanism to explain the pathogenesis of GDM.

GLP levels (pmol/l)	GDM	Controls	Adj p-value$^{BMI, age, ethnicity, smoking}$
GLP_{0min}	13.6±4.46	15.7±4.08	NS
GLP_{30min}	15.9±3.89	19.8±4.52	0.041
GLP_{60min}	18.1±4.96	20.6±4.44	NS
GLP_{90min}	18.3±4.49	20.2±4.84	NS
GLP_{120min}	18.2±4.61	18.8±4.66	NS

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Obesity, Diabetes & Thyroid

Clinical Endocrinology Trust Prizes

OC3.1

Perchlorate exposure affects thyroid function in third trimester pregnant women from South-West England

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Introduction
Iodine is important for thyroid hormone synthesis, and iodine deficiency in pregnancy may impair foetal neurological development. Perchlorate, found in some foods and everyday chemicals (e.g. fertilisers) and thiocyanate, which is found in cigarette smoke, decrease the transport of iodine from the circulation to the thyroid cells by inhibiting the sodium-iodide symporter. Environmental exposure to these substances during pregnancy may result in reduced thyroid hormone synthesis. Therefore, we aimed to explore the impact of perchlorate and thiocyanate exposure on thyroid status in a cohort of pregnant mothers from South-West England.
Methods
Urine samples were obtained from 308 women participating in a study of breech presentation in late pregnancy. They had no known thyroid disease and a singleton pregnancy at 36–38 weeks gestation. Samples were analysed for urinary concentrations of iodine (UIC), perchlorate (UPC) and thiocyante (UTC). Blood samples were taken for free T4 (FT4), thyrotropin (TSH), thyroid peroxidase antibodies (TPO-Ab). Baseline data included: age, parity, smoking status, ethnicity, BMI at booking. Variables were assessed for normality and natural log transformed where appropriate.
Results
Participants had a mean (SD) age 31(5) years, median (IQR) BMI 24.4(22.0, 28.3) kg/m^2, and median (IQR) UIC 88 (55, 158) mcg/l. 42% were primiparous, 10% were smokers, and 96% were Caucasian. Log transformed UPC was negatively correlated with FT4 in the whole cohort ($n=308$, $r=-0.12$, $p=0.03$) and in the subgroup of women with UIC <100 mcg/l ($n=174$, $r=-0.15$, $P=0.04$). Regression analysis with the potential confounders, smoking, TPO-Ab status, UIC and UTC, identified UPC to be negatively associated with FT4 ($P=0.04$). UPC was not associated with TSH, and UTC was not associated with FT4 or TSH.
Conclusion
Environmental perchlorate exposure is negatively associated with circulating FT4 levels in third trimester pregnant women. This may have an adverse impact on neurocognitive development of the fetus.

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OC3.2

Hypothyroidism is a risk factor for acquiring diabetes in women with Turner Syndrome

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Introduction
The adult Turner Syndrome (TS) clinic at UCLH has collected data on over 800 women, attending for up to 20 years comprising over 8000 clinic visits. Data from this cohort forms the Turner Life Course Project. This large dataset allows analysis of pathogenesis of common chronic conditions including diabetes mellitus (DM) and hypothyroidism. There is some debate about the classification of DM associated with TS, with an over representation of up to 11-fold of type 1 and 4-fold of type 2 forms. Diabetes related autoantibodies and insulin resistance are not prominent in adults with TS and diabetes. In this study we present an analysis of the factors associated with DM in adult women with TS.
Methods
We performed a retrospective analysis of 565 women with TS in whom DM status was confirmed. TS health surveillance parameters were compared in those with DM to those without. Factors affecting DM risk included karyotype, age, BMI, hypothyroidism, streatohepatitis and congenital heart disease. Binary regression analysis was performed in order to assess interaction between variables.
Results
Diabetes had been diagnosed in 46/565 (8%) of women with TS in whom the mean age was 43.7 years compared to 32.9 years without DM. DM was associated with older age, a higher BMI, raised liver enzymes and hypothyroidism compared to non-diabetics ($P=<0.05$). Hypothyroidism was present in 11.7% of women with TS and DM compared to 4.7% of those without ($P=0.01$). Hypothyroidsim remained an independent association, when controlled for age and BMI and could not be accounted for by differences in TSH concentrations.
Conclusions
The association between hypothyroidism and DM in women with TS raises the possibility that autoimmunity is of greater importance in the pathogenesis of DM than had previously been recognised, in spite of lack of DM related autoantibodies previously reported.

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OC3.3

The GLP-1R agonist exendin-4 reduces cerebrospinal fluid secretion and intracranial pressure

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Background
Current therapies for reducing raised intracranial pressure (ICP) in conditions such as idiopathic intracranial hypertension have limited efficacy and tolerability. As such, there is a pressing need to identify novel drugs. Glucagon-like peptide-1 receptor (GLP-1R) agonists are used to treat diabetes and promote weight loss but have also been shown to affect fluid homeostasis in the kidney. Here, we investigate whether exendin-4, a GLP-1R agonist, is able to modulate cerebrospinal fluid (CSF) secretion at the choroid plexus and subsequently reduce ICP.
Methods
GLP-1R mRNA and protein was assessed in human and rat choroid plexus. The effect of exendin-4 on GLP-1R activation and CSF secretion was evaluated in cultured rat choroid plexus epithelial cells using cAMP assays and a Na^+K^+ ATPase activity assay. The effect of Exendin-4 on ICP was assessed in adult female rats with normal and raised ICP.
Results
We demonstrated that the GLP-1R is present in human and rat choroid plexus. Exendin-4 significantly increased cAMP levels (2.14 ± 0.61 fold, $P<0.01$), part of the GLP-1R signalling pathway, and significantly reduced Na^+K^+ ATPase activity, a marker of CSF secretion ($39.3 \pm 9.4\%$ of control; $P<0.05$). *In vivo* ICP recording in adult rats demonstrated that subcutaneous administration of exendin-4 significantly reduced ICP in normal ($65.2 \pm 6.6\%$ of baseline; $P<0.01$) and raised ICP rats ($56.6 \pm 5.7\%$ of baseline; $P<0.0001$). In addition, the effects of a single subcutaneous injection of exendin-4 lasted for 24 hours and daily exendin-4 administration had a cumulative effect on reducing baseline ICP.
Conclusion
We demonstrate that Exendin-4 reduces CSF secretion by the choroid plexus and ICP in normal rats and rats with raised ICP. Repurposing existing GLP-1R agonists may represent a novel therapeutic strategy for conditions of raised ICP such as idiopathic intracranial hypertension.

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OC3.4

Neutrophil elastase-mediated regulation of adipose glucocorticoid exposure through CBG cleavage

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Adipose exposure to glucocorticoids (GCs) results in visceral adiposity and insulin resistance. Only the unbound, free fraction of GC can diffuse into cells. Corticosteroid binding globulin (CBG) is the major GC carrier, binding 80–85% of circulating GCs with high affinity. Targeted proteolysis of CBG by neutrophil elastase (NE) significantly reduces CBG binding affinity. This suggests that neutrophil-mediated inflammation provides a regulatory mechanism for delivery of GCs to target tissues. In obesity, elevated NE activity is observed in plasma alongside adipose neutrophil infiltration. Strikingly, mice deficient in neutrophil elastase (ELA-KO) fed a high-fat diet display improved whole body insulin sensitivity and adipose insulin signaling, which we hypothesized is mediated by reduced release of GC from CBG within adipose. Male ELA-KO mice and littermate controls (8–10 weeks) were fed a high-fat diet (60% fat) for 10 weeks. Compared to controls, ELA-KO mice gained less weight, had reduced fat mass (8.1 ± 0.9 vs 5.3 ± 0.7 g; $P=0.022$), and displayed improved glucose tolerance ($P=0.017$, Two-way repeated measures ANOVA). Plasma CBG binding capacity, measured by ligand saturation assay, was greater in ELA-KO mice compared to controls (197 ± 14 vs 156 ± 12 nM; $P=0.04$). Despite no difference in total plasma corticosterone concentrations, mesenteric adipose corticosterone levels, measured by LC-MS/MS, were significantly reduced in ELA-KO mice compared to controls (28.6 ± 5.9 vs 56.1 ± 11.3 pg/mg; $P=0.037$). These data provide the first direct evidence that NE influences CBG binding capacity *in vivo*. Moreover, this is accompanied by lower GC levels in adipose tissue but not plasma, suggesting that changes in CBG binding capacity at sites of inflammation alter local tissue GC exposure by influencing the free GC fraction. This opens the possibility of NE as a therapeutic target to regulate adipose tissue GC exposure in obesity and metabolic syndrome.

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OC3.5

Increased global long interspersed nucleotide element 1 DNA methylation in type 2 diabetes mellitus individuals relates to lower blood pressure and BMI

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Introduction
T2DM is one of the main causes of morbidity and mortality in the UK. Epigenetic mechanisms impact gene expression and could predispose individuals to a particular metabolic phenotype. We investigated association of LINE-1 methylation (a surrogate of global DNA methylation) with cardiometabolic parameters in a longitudinal cohort of T2DM patients.
Methods
Global LINE-1 DNA methylation in blood-derived DNA samples from 795 (men 60%, women 40%) T2DM patients was quantified by pyrosequencing using PyroMark Q96 CpG LINE-1 (Qiagen). Mean age 59.2 years (men 58.6 years, women 60.0 years). Longitudinal data was collected from year 2002 to 2016.
Results
Mean methylation quantified at 4 CpG sites was $75.78 \pm 3.37\%$. There was no significant methylation difference between men $75.93 \pm 3.33\%$ and women $75.56 \pm 3.41\%$, $P=0.130$ or by age ($P=0.123$). Cross-sectional analysis at baseline year 2002: Linear regression analysis at baseline showed LINE-1 methylation could statistically significantly predict diastolic BP (adjusted coefficient -0.35 (95% CI -0.59 – -0.11, $P=0.004$)) and eGFR (-0.55 (95% CI -0.92 – -0.18, $P=0.004$)). A ten percent increase in LINE-1 methylation resulted in reduction of diastolic BP by 3.5 mmHg and a reduction in eGFR by 9.2 ml/min/1.73 m^2. There was no association with lipid parameters or with HbA1c. Longitudinal analysis over 14 years: Global LINE-1 methylation was negatively associated with BMI in women (-0.25 (95% CI -0.45 – -0.05, $P=0.013$)), and with less weight gain over time. A ten percent increase in LINE-1 methylation was associated with 2.5 kg/m^2 reduced BMI in 2016 compared with the population mean. The relation with BP diminished over time, likely due to 'treatment to target' effects. Logistic regression analysis showed no association with mortality and cardiovascular events.
Conclusion
In a 14 year longitudinal cohort of T2DM individuals, we have demonstrated that higher degree of LINE-1 methylation is predictive of less weight gain over time/lower future BMI in women, and relates to lower baseline diastolic BP. Methylation status may thus influence weight trajectory in this group. Potential effects of pharmacological intervention on the relation between methylation and BP/eGFR require further investigation.

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OC3.6

Identification of novel sodium iodide symporter interactors which modulate iodide uptake

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By exploiting the canonical function of the sodium iodide symporter (NIS), ablative radioiodide therapy is an effective treatment for thyroid cancer. However, a subset of patients are unable to accumulate sufficient radioiodide due to decreased expression and/or plasma membrane localisation of NIS. Radioiodide therapy has been proposed as a viable treatment for breast cancer, but is hampered by low levels of NIS membrane localisation. Currently, the regulation of NIS trafficking to the plasma membrane is ill-defined. Mass spectrometry was performed on proteins co-immunoprecipitating with lentivirally expressed NIS in whole cell and plasma membrane extracts. NIS function was assessed following knockdown, overexpression and pharmacological inhibition of shortlisted interactors using radioiodide uptake assays. Interactors were validated by co-immunoprecipitation and proximity ligation assays. NIS activity was significantly altered by ADP-ribosylation factor 4 (ARF4) and valosin containing protein (VCP) in TPC1 thyroid and MDA-MB-231 breast cancer cells lentivirally-expressing NIS. ARF4 downregulation decreased radioiodide uptake by 75 and 44%, and VCP downregulation increased radioiodide uptake by 71 and 56%, in thyroid and breast cells, respectively. Transient overexpression of these genes significantly reversed siRNA effects on NIS function. Co-immunoprecipitation assays confirmed NIS interacts with ARF4 and VCP *in vitro*, and proximity ligation assays revealed the subcellular sites of interaction. TCGA data analysis of 58 matched papillary thyroid cancers revealed ARF4 was significantly repressed and VCP highly upregulated in thyroid cancer, providing a putative explanation for repressed NIS function. Pharmacological inhibitor studies demonstrated Eeyarestatin-1 and NMS-873 could overcome VCP inhibition of NIS function, implicating the endoplasmic reticulum-associated degradation pathway as critical to NIS processing. Further, we identified that NIS is ubiquitylated *in vitro*, and suggest this as the possible mechanism through which VCP alters NIS function. These studies thus identify two new potential therapeutic targets for enhancing radioiodide uptake in patients with radioiodide-refractory thyroid cancer.

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Adrenal and Steroids

OC4.1

Predicted benign and silent SNPs in *CYP11A1* cause primary adrenal insufficiency through missplicing

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Background
CYP11A1 encodes the P450 side chain cleavage enzyme (P450scc) responsible for initiating steroidogenesis and classically gives rise to disordered sex development plus adrenal and gonadal insufficiency. The rs6161 variant in exon 5 of *CYP11A1* (c.940G>A; p.E314K) has previously been considered as 'benign'. When next generation sequencing was performed in patients with primary adrenal insufficiency of unknown etiology the rs6161 variant was found as a heterozygous change in 15 subjects (minor allele frequency 0.0625 (our cohort) vs 0.0024 (ExAC database)). In 13 patients the c.940G>A variant occurred in trans with a second clearly disruptive heterozygous change, in the remaining two patients the only other novel variant was a synonymous substitution (c.990G>A (p.T330=), c.1173C>T (p.S391=)). Given the enrichment of the c.940A allele and rarity of the two synonymous variants c.990A and c.1173T (MAF 0 and 3×10^6 respectively), we suspected they were pathogenic and therefore investigated their effects on mRNA processing and/or protein function.
Results
An *in vitro* splicing assay demonstrated aberrant splicing for all three variants, causing exon 5 skipping in most RNA transcripts for variants c.940A and c.990A and complete exon 7 skipping for c.1173T. In each instance when the exon is skipped a frameshift and premature translation-termination codon will occur. We corroborated the findings for variants c.940A and c.990A *in vivo* in patient samples. Mutant p.314K P450scc enzyme activity did not differ from WT in a validated functional assay in *E. coli*. However, when expressed in a eukaryotic cell line the mutant protein is truncated to 30-35 kDa, and the half-life is much shorter than for WT.
Conclusion
This comprehensive analysis illustrates how multiple mechanisms might contribute to loss-of-function and highlights the fact that *in silico* prediction tools are inadequate. Therefore functional analyses need to be undertaken on all rare variants to determine pathogenicity and correctly assign clinical significance.

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OC4.2

Glucocorticoids rapidly inhibit cell migration through a novel, non-transcriptional pathway involving HDAC6

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Glucocorticoids (Gc) act through the glucocorticoid receptor (GR) to regulate immunity, energy metabolism, and tissue repair. The inactive GR is held in the cytoplasm in a multi-protein complex, which upon ligand binding undergoes a conformational change. Activated GR translocates to the nucleus to regulate gene expression (over hours), but some effects occur more rapidly. Gc inhibit cell migration through an uncertain mechanism. We now show a very rapid effect, and surprisingly find the GR agonist Dexamethasone, and antagonist, RU486, are equipotent. The migration effect was prevented by GR knockdown, confirming GR specificity, but not by actinomycin D treatment, suggesting a non-transcriptional mechanism. To investigate the Gc effect we analyzed microtubule network kinetics using plus end microtubule real time assays, which revealed Gc induction of tubulin acetylation – a marker of microtubule stability. Inhibition of the cytoplasmic deacetylase HDAC6, which deaceylates tubulin, mimicked the Gc effect, and HDAC6 overexpression rescued the Gc effect, implicating HDAC6 as a Gc effector. We found interaction between GR and HDAC6, using fluorescent cross correlation spectroscopy, and showed HDAC6 nuclear translocation following Gc treatment. We propose that Gc treatment displaces HDAC6 from cytoplasmic microtubules and therefore restricts interaction with it substrate, driving increased tubulin acetylation, increasing stability of the microtubule network and reducing cell motility. We propose that Gc treatment displaces HDAC6 from cytoplasmic microtubules and therefore restricts interaction with it substrate, driving increased tubulin acetylation, increasing stability of the microtubule network and reducing cell motility. We therefore discover a novel, non-transcriptional mechanism whereby GR agonists and antagonists, through actions on HDAC6, rapidly reorganize cell architecture to change cell function.

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OC4.3

Local reactivation of glucocorticoids by 11β-HSD1 mediates their detrimental effects on bone

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Glucocorticoids (GCs) have potent immunomodulatory and anti-inflammatory effects and are widely used in the treatment of inflammatory diseases. Unfortunately, their long term administration causes serious systemic metabolic side effects including osteoporosis, muscle wasting and insulin resistance. 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) is responsible for the local conversion of inactive GCs to their active counterparts. It has been shown that many of the metabolic side effects associated with GC excess are mediated by local reactivation by 11β-HSD1. We hypothesised that 11β-HSD1 within osteoblasts mediates the destructive effects of GCs on bone. Wild-type (WT) mice and transgenic mice lacking 11β-HSD1 (11βKO) were treated with the active GC corticosterone (CORT) (100 mg/ml) for 4 weeks. Tibia and humerus bones were excised post-mortem for micro-CT analysis and three point flexure strength tests, respectively. Micro-CT analysis of bone volume to tissue volume (BV/TV), trabecular thickness (TT) and trabecular number (TN) found no significant differences between untreated WT and 11βKO mice (BV/TV: WT 8.5% ± 0.66 vs 11βKO 7.5% ± 0.76, NS; TT: WT 96.5 μm ± 3.8 vs 11βKO 95.8 μm ± 6.4, NS; TN: WT 0.0009 1/μm ± 0.00004 vs 11βKO 0.0008 1/μm ± 0.00004, NS). Humerus bone strength (HBS) of WT and 11βKO animals also showed no significant differences (WT 51.2 MPa ± 15.1 vs 11βKO 49.2 MPa ± 4.9, NS). All bone parameters were decreased in CORT fed WT mice indicating the development of osteoporosis, whilst 11βKO mice were protected against many of the detrimental effects of CORT (BV/TV: WT 4.2% ± 0.38 vs 11βKO 7.2% ± 0.71, $P \leq 0.05$; TN: WT 0.0006 1/μm ± 0.00004 vs 11βKO 0.0009 1/μm ± 0.00008, $P \leq 0.001$; HBS: WT 27.1 MPa ± 5.6 vs 11βKO ± 50 MPa ± 5.1, $P \leq 0.05$). These data suggest that local reactivation of GCs by 11β-HSD1 mediates the development of glucocorticoid-induced osteoporosis.

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OC4.4

The role of "stress" in aldosterone-mediated hypertension: circumstantial evidence from the "stress subtraction" experiment of adrenal vein sampling

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Background
Primary aldosteronism (PA) accounts for a significant proportion of patients with hypertension. There has been a focus on ACTH in the pathogenesis of aldosterone secretion even with suppressed renin. With the link between psychological stress and cardiovascular disease as well as the association between anxiety and PA, there may be broader neurohormonal "stress" stimuli that modulate aldosterone production in PA patients, beyond the HPA axis. PA patients who undergo adrenal venous sampling (AVS) receive sedation with narcotic and benzodiazepine. This induces a state of relaxation ("stress subtraction") and permits observation of plasma aldosterone levels in such a setting.
Hypothesis
Dampening the neurohormonal stress response via narcotic/benzodiazepine results in a decrease in aldosterone production even among PA patients.
Patients
One hundred and thirty-one subjects undergoing AVS for PA (University of Calgary). 78 PA-AVS patients from University of British Columbia served as an independent confirmatory cohort.
Methods
Post narcotic/benzodiazepine morning IVC aldosterone (IVC-A) levels were compared to morning aldosterone levels drawn as an outpatient for the diagnosis of PA. IVC-A levels were correlated with IVC cortisol levels pre and post cosyntropin.
Results
Median AVS-IVC-A levels were significantly lower than outpatient measures (278 pmol/l vs 468 pmol/l, $P < 0.001$). 72% of PA subjects had IVC-A levels more than 30% lower than outpatient measures. While the correlation between IVC-A and IVC cortisol was poor at baseline and post cosyntropin, the proportional rise in IVC-A and IVC- cortisol was modestly correlated ($r = 0.32$, $P < 0.001$). Repeat analysis on the UBC cohort produced nearly identical results (median 210 pmol/l vs 568 pmol/l, $P < 0.001$) with 88% having IVC-A > 30% lower than the outpatient aldosterone.
Conclusions
Most PA patients have markedly lower IVC-A levels during AVS compared to those found during first outpatient diagnosis. In the absence of confounding medications, hypokalemia, circadian timing, postural variation and with low correlation to cortisol, this suggests alternate input from the CNS upon aldosterone secretion in PA.

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OC4.5

NAD+ availability modulates 11β-HSD1 mediated glucocorticoid regeneration in mouse skeletal muscle

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11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) is an NADPH-dependant oxo-reductase located in the sarcoplasmic reticulum (SR) lumen of skeletal muscle. It generates active glucocorticoids to regulate permissive and adaptive metabolism. Hexose-6-phosphate dehydrogenase (H6PD) interacts with 11β-HSD1 to generate an appropriate NADPH/NADP+ ratio to support activity. H6PD depletion impairs SR NADPH generation triggering 11β-HSD1 to assume glucocorticoid inactivating dehydrogenase activity. We tested whether modulating cellular nicotinamide adenine dinucleotide (NAD+) availability (parent molecule of NAD(P)(H)) influenced 11β-HSD1 activity in muscle. We used FK866 to inhibit nicotinamide phospho-ribosyltransferase (NAMPT, rate-limiting enzyme in NAD+ biosynthesis) to deplete NAD(P)(H) in mouse and primary myotubes. 48 h FK866 treatment impaired cellular energetic status, reducing NAD+ (>90%), NADP+ (>50%) and ATP (>30%) without limiting cell viability. 11β-HSD1 reductase activity was decreased to 30% that of untreated cells (152 ± 18 vs 512 ± 44 pmol/mg protein/h respectively, $P < 0.005$). Furthermore, NADP+-dependent 11β-HSD1 dehydrogenase (glucocorticoid inactivation), as seen in H6PDKO myotubes, is also impaired following NAMPT inhibition. The NAD+ precursor nicotinamide riboside (NR, 0.5 mM), which bypasses NAMPT inhibition, restored NAD+ levels and rescued 11β-HSD1 oxo-reductase activity in wild-type and dehydrogenase activity in H6PDKO myotubes. 11β-HSD1 activity normalised in as little as 30 min after NR treatment. To examine the *in vivo* relevance, FK866 (10 mg/kg) was administered intraperionteally to wild-type mice for 72 h which depleted NAD+ in skeletal muscle and liver, however, 11β-HSD1 activity only decreased in muscle compared to untreated mice (137 ± 5.55 vs 83.78 ± 3.014 pmol/mg/h, $P < 0.001$), with the liver unaffected. These data suggest that a cross talk exists between the cytosol and the SR which can impact redox status and modulate 11β-HSD1 mediated glucocorticoid regeneration in skeletal muscle. Furthermore, NAMPT inhibition is being studied as a potential anti-cancer therapy and these data reveal hitherto unanticipated effects this therapy may have in a range of tissues.

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OC4.6

Distinct patterns of glucocorticoid metabolism in patients with HNF1A-MODY have the potential to confer a beneficial metabolic phenotype

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Background and aims
HNF1A-MODY causes monogenic diabetes with a lean, insulin sensitive phenotype. Altered glucocorticoid (GC) metabolism has been implicated in the pathogenesis of type 2 diabetes (T2D) and inhibitors of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) which regenerates active cortisol from inactive cortisone have been trialled as a therapeutic approach. 11β-HSD1 is down-regulated in hepatocytes from *Hnf1a* knock-out mice but the role of pre-receptor GC metabolism in HNF1A-MODY has not been explored. We hypothesised that those with HNF1A-MODY would have a distinctive pattern of GC metabolism that may underpin aspects of their metabolic phenotype.
Subjects and methods
Urinary steroid metabolites were measured by gas chromatography mass spectrometry in 35 subjects with HNF1A-MODY and compared to 35 individuals with T2D and 35 non-diabetic controls. Groups were age- and BMI-matched. Results were analysed separately for men and women due to gender dimorphism of urinary steroids.
Results
11β-HSD1 activity, assessed by the ratio of urinary (tetrahydrocortisol + 5α-tetrahydrocortisol): tetrahydrocortisone was not different between the groups. However, the activity of 11β-HSD2, which deactivates cortisol and is defined by the ratio of urinary cortisol: cortisone, was reduced in patients with HNF1A-MODY and T2D compared to non-diabetic controls (Kruskal-Wallis: $P=0.007$ men; $P=0.02$ women). The reduction in renal 11β-HSD2 activity in HNF1A-MODY and T2D resulted in a significant increase in urinary free cortisol compared to non-diabetic controls ($P=8.7\times10^{-5}$ men; $P=0.003$ women). We also detected an increase in the activity of 5β-reductase (which inactivates cortisol to 5β-dihydrocortisol decreasing cortisol availability) in HNF1A-MODY compared to T2D subjects ($P=0.004$ men; $P=0.005$ women). There was no difference in the activity of 5β-reductase between T2D and non-diabetic controls.
Conclusions
Subjects with HNF1A-MODY have enhanced cortisol clearance through the increased activity of 5β-reductase. This has the potential to decrease local glucocorticoid availability and may result in improved metabolic phenotypes as compared to those with T2D.

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Reproduction and Neuroendocrinology

OC5.1

Increased sertoli cell proliferation and sperm production in FSTL3 deleted mice

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Male problems such as oligospermia, azoospermia among others, affect around 30% of infertile couples. Male fecundity relies on the production of large numbers of spermatozoa which is dependent on the number of Sertoli cells. Activin and related TGFβ family ligands regulate testicular development and function. Follistatin Like-3 (FSTL3) is a glycoprotein that binds and inhibits activin. FSTL3 deletion in mice leads to increased adult testicular size with concurrent increase in Sertoli and germ cell numbers. Also age-related testicular regression is delayed in FSTL3 KO mice. Our current investigation show that the testicular size/body ratio of FSTL3 KO mice is similar to WT at weaning (3 weeks) but 1.5 fold increased by 17 weeks. We therefore hypothesized that, while Sertoli cell number is similar between the two genotypes early in life, with age the number of Sertoli cells and concomitantly the germ cell components of the FSTL3 KO mice increase compared to WT. To begin to investigate testicular cell proliferation we performed BrdU incorporation and monitored PCNA expression in FSTL3 KO and WT testes before (3 week) and after (8 week) the onset of the first wave of spermatogenesis. Whereas BrdU incorporation and PCNA expression at 8 weeks is similar between the two genotypes, at 3 weeks FSTL3 KO mice showed significantly increased incorporation of BrdU and expression of PCNA compared to WT. In addition, while sperm count is similar in mice aged 38 weeks from both genotypes, there is an 8 fold greater sperm count in FSTL3 KO mice aged 91 weeks compared to their WT counterpart. Taken together, our findings therefore support the idea that FSTL3 deletion leads to Sertoli cell proliferation beyond the stages of somatic expansion compared to WT mice. Currently we are investigating whether these phenotypes are associated with improved male fertility.

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Clinical Endocrinology Trust Prizes

OC5.2

Kisspeptin modulates resting brain activity to alter responses to negative stimuli in humans

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Kisspeptin is a crucial activator of reproductive function, stimulating GnRH neurons in the hypothalamus. However, kisspeptin and its receptor are also expressed in other brain regions including the limbic system, which has key roles in emotional processing. Kisspeptin signalling in the limbic system modulates emotional and sexual brain processing during tasks, however the effects of kisspeptin on underlying resting brain activity have not yet been studied. This is vital for our understanding of reproductive physiology and development of kisspeptin therapeutics. We hypothesised that kisspeptin administration modulates resting brain activity and influences responses to emotional stimuli. To test this, we investigated the effects of kisspeptin administration on brain activity and mood in men. We mapped brain activity using functional MRI in 29 healthy men (mean age 25.0±0.9 years) using a randomised blinded two-way placebo-controlled protocol. The effects of kisspeptin on resting state activity and brain region connectivity were assessed, and correlated to subsequent responses to emotional stimuli and psychometric outcomes. Kisspeptin administration resulted in an increase in circulating kisspeptin ($P<0.001$) but not testosterone ($P=0.180$) during the scans, as expected. Kisspeptin enhanced connectivity between key limbic brain structures, including between the hippocampus-caudate ($P<0.05$) and hippocampus-globus pallidus ($P<0.001$); structures with established roles in mood regulation and which express kisspeptin receptors. Furthermore, kisspeptins enhancement of resting hippocampus-globus pallidus connectivity predicted increased responses to visual-evoked negative stimuli in several limbic structures (including the thalamus, accumbens, putamen, and cingulate (all $P<0.01$)). Collectively, these data provide evidence that kisspeptin modulates underlying limbic brain activity and influences subsequent brain responses to negative stimuli. This is the first report of a novel role for kisspeptin in the integration of resting brain activity, negative emotional processing, and reproduction in humans. Therefore, these data have important implications as they suggest that kisspeptin may modulate negative mood with potential therapeutic relevance.

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OC5.3

Decoding the functional significance of follicle stimulating hormone glycosylation variants

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FSH and its G protein-coupled receptor (FSHR) are essential for the coordination of reproductive functions. As such, they are a primary target of most assisted reproductive technologies, thus understanding the physiology regulating their function is paramount. Two naturally occurring glycoforms of FSH have been identified-hyperglycosylated FSH (FSH24) and hypoglycosylated FSH (FSH21), based on their ASN glycosylation pattern. The secretion of FSH21 and FSH24 has been shown to be differentially regulated during the menstrual cycle, suggesting functional dichotomy of FSH21 and FSH24 within the ovary. Additionally, FSH24 and FSH21 display differential binding kinetics to FSHR and potency at activating cAMP, the principle G protein-dependent pathway of FSH/FSHR, suggesting an important role for the differential actions and activities of FSH glycoforms in regulating FSHR function. This study aimed to (1) determine how the differential effects of FSH21 and FSH24 are mediated by the FSHR, and (2) determine additional differential signalling pathways/novel targets of FSH21 and FSH24. As we have previously shown di/oligomerisation of the luteinising hormone receptor to be an important modality for regulating signal strength, we determined if FSH21 and FSH24 differentially modulated FSHR

di/oligomerisation via the super resolution imaging technique, photoactivated dye-localisation microscopy. In HEK293 cells transiently expressing FSHR, acute 2-minute treatment with 30 ng/ml FSH21 resulted in a significant decrease in the number of FSHR homomers observed in comparison to basal, however, no signficant difference from basal was observed with FSH24 treatment. Analysis of the individual FSHR homomeric forms revealed an enrichment in dimeric population and decrease in higher order FSHR oligomers following FSH21-treatment, suggesting the enhanced signalling properties of FSH21 may be mediated by alterations in FSHR associations. Phosphokinase screening identified novel differential targets of FSH21 and FSH24. These data support the distinct roles of FSH glycoforms and suggest this may be mediated via modulating FSHR di/oligomerisation.

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OC5.4

Reactive oxygen species as a novel metabolic pathway for sperm DNA damage and Recurrent Pregnancy Loss

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Background
Recurrent pregnancy loss (RPL) affects 1–2% couples, and is defined as $\geqq 3$ consecutive pregnancy losses before 20-weeks' gestation. RPL is caused by foetal chromosomal abnormalities, or maternal factors such as thrombophilia. It was recently reported that men with RPL have high levels of sperm DNA fragmentation (a marker of infertility); however, the cause of this damage is currently not known. Seminal plasma has high levels of granulocyte-derived oxidative stress to prevent bacterial infection; however, sperm are also susceptible to oxidative stress. Oxidative stress may therefore play a role in male factor RPL.
Aims
Measure seminal reactive oxidative stress (ROS) and sperm DNA fragmentation in men with RPL vs. age- and BMI-matched controls.
Methods
Following ethical approval, seminal ROS was measured using a previously described in-house luminol chemiluminescence assay in men with RPL ($n=47$) and men unaffected by RPL ($n=63$). Sperm DNA fragmentation was measured using Halosperm assay.
Results
Men with RPL had similar mean age, weight and BMI compared with controls. Men with RPL had 50% higher ROS levels compared with controls (median ROS (IQR) (RLU/sec/10^6sperm): 0.8 (1.3), controls; 1.3 (3.8), RPL; $P<0.01$). Men with RPL had a four-fold higher risk of ROS elevation compared with controls (5/63, controls; 16/47, RPL, $P=0.001$). Sperm DNA fragmentation was 80% higher in men with RPL compared with controls (median DNA fragmentation (IQR) (%): 6.0 (8.0), controls; 11.0 (7.5); $P<0.05$). Men with RPL were significantly more likely to have abnormal sperm morphology compared with controls.
Conclusions
Our data show for the first time that men with RPL have increased seminal oxidative stress, which is known to cause DNA damage and reduced function in sperm. Seminal ROS presents a novel diagnostic tool and potential novel metabolic pathway for treating couples with RPL. These data therefore have important potential clinical implications for couples affected by RPL.

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OC5.5

Vitamin-D and fetomaternal immunity: next generation RNA sequence analysis reveals unique effects upon uterine natural killer cells

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Vitamin D deficiency is prevalent in pregnant women and associated with adverse pregnancy outcomes, including pre-eclampsia. Active vitamin-D (1,25(OH)2D3) exerts important non-classical immune-regulatory effects, and the maternal placenta (decidua) appears a key target. Uterine natural killer cells (uNKs) are the most prominent decidual immune cell during early pregnancy. Given their critical role in fetal implantation and placentation, we hypothesised uNKs are a local source and pivotal target for 1,25(OH)2D3. CD56+ uNK and peripheral NKs (pNKs) were isolated from paired-decidua and blood from pregnant women undergoing 1st trimester surgical termination. NKs were cultured $\pm$ cytokine-stimulation (CK) $\pm$1,25(OH)2D3 (10 nM). uNK and pNKs express the vitamin D-activation enzyme CYP27B1 and receptor (VDR), with both up-regulated by CK ($P<0.05$). Addition of 1,25(OH)2D3 attenuated this response ($P<0.05$), with concomitant up-regulation of CYP24A1. RNA sequence analysis (RNAseq) was performed for unbiased identification of 1,25(OH)2D3 targets using FACS sorted uNK and pNKs cultured with CK $\pm$1,25(OH)2D3. The transcriptional patterns of NKs are highly tissue-specific; overall 2286 genes (1098 up-, 1188 down-regulated) were differentially expressed (DE) ($P\leq 0.05$, fold-change -0.5 to $+1.5$) in CK uNK and pNKs. For uNKs, 66 genes were DE (46 up-, 20 down-regulated) with 1,25(OH)2D3 comparative to CK alone. For pNKs, 71 were DE with 1,25(OH)2D3 (38 up-, 33 down-regulated). Only TRIM35, which inhibits cell proliferation and is anti-tumorigenic, was up-regulated in both Unk ($P=0.0006$, fold-change -1.86) and pNKs ($P=0.01$, fold-change -1.50). A unique transcriptional profile was identified in uNKs, with 1,25(OH)2D3-mediated effects upon genes associated with metabolism, migration, adhesion and apoptosis. Notably, 1,25(OH)2D3 increased galectin-9 ($P=0.01$, fold-change 1.75), which drives pNK transformation towards a decidua-phenotype, and SERPINB1, potent granzyme inhibitor ($P=0.002$, fold-change 2.37). NKs contain a functional vitamin D metabolic system, which appears particularly sensitive to 1,25(OH)2D3 within the decidua. RNAseq revealed a unique repertoire of 1,25(OH)2D3 targets, which appear highly relevant to decidualisation and materno-fetal tolerance.

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OC5.6

The MAPK effector B-Raf is essential for hypothalamic–pituitary axis development and activating mutations in *BRAF* cause congenital hypopituitarism

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Somatic activating mutations in *BRAF*, encoding B-Raf, have been described in tumours and recently craniopharyngiomas. Germline mutations in *BRAF* and other components of the RAS/MAPK pathway are found in RASopathies, whose features include endocrine deficiencies but not craniopharyngiomas. We report three *BRAF* mutations (two of which are novel) in four children with congenital hypopituitarism. To demonstrate the functional role of the three variants we assessed the levels of phosphorylated ERK as a readout of RAS/MAPK pathway activity and performed phosphoproteomic analyses using Mass Spectrometry. We identified that the *BRAF* mutations increase levels of phosphorylated ERK and significantly increase B-Raf kinase activity resulting in hyper-phosphorylation of members of the RAS/MAPK and the JAK/STAT pathways demonstrating that the *BRAF* genetic variants are activating mutations. To further demonstrate the role of activated RAS/MAPK pathway in hypopituitarism, we used a murine transgenic approach to express the activating *Braf* V600E mutation using a pituitary-specific Cre reporter line, *Prop1:Cre*. Genotypes of offspring from *Prop1:Cre* x $Braf^{V600E/V600E}$ genetic crosses showed a significant deviation from the expected Mendelian ratio, indicating embryonic lethality. $Prop1:Cre;Braf^{V600E/+}$ pups exhibited dwarfism and premature death suggesting a functional compromise of the HP-axis. Pituitary specification markers such as *Lhx3, Pitx1* and *Hesx1* were found to be appropriately expressed during early embryogenesis. However, pituitary glands exhibited hyperplasia with multiple clefts due to an increase in mitotic index at E11.5 and E13.5 ($P<0.01$). Immunohistochemistry at E16.5 revealed impaired terminal differentiation of hormone-producing cells with an increase in ACTH and prolactin but absence of all other hormone-producing cells.

Our data demonstrate that activating *BRAF* mutations present during pituitary development lead to congenital hypopituitarism both in mouse and humans. Our findings relate mutations in the RAS/MAPK pathway to pituitary abnormalities and suggest that activating *BRAF* mutations in pituitary stem cells during embryogenesis do not cause tumours.

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Clinical Endocrinology Trust Prizes

Bone, Calcium and Neoplasia

OC6.1

Photoperiod-induced central actions of thyroid hormone are essential for medullary bone formation

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Seasonal reproduction enables animals outside tropical regions to rear offspring in a favourable environment. Increasing day length triggers a hypothalamic relay involving thyrotropin, the type 2 deiodinase enzyme and thyroid hormone, which activates the hypothalamic-pituitary-gonadal axis to induce reproductive competence. Photoperiod regulates calcium metabolism and the egg-laying cycle in the Japanese quail (*Coturnix japonica*), and we hypothesised that activity of this relay would have major consequences for bone mineralisation and strength. Quails were housed in long (20 h light, 4 h dark) or short (6 h light, 18 h dark) day conditions for up to 12 weeks and skeletal consequences were determined by X-ray microradiography, micro-CT, electron microscopy, histomorphometry and biomechanical testing ($n=10$ per sex, per group). Both ovary and testis weights increased >10-fold ($P<0.001$, ANOVA) after long day compared to short day exposure. Long day exposure in females resulted in massive increases in bone mineral content and mineralisation ($P<0.001$, Kolmogorov-Smirnov test), and bone strength and stiffness ($P<0.001$, ANOVA), as a consequence of medullary bone formation. By contrast, medullary bone was absent in females exposed to short day length and never seen in males. Medullary bone was a highly vascular and dynamic tissue, characterised by osteoclast resorption pits and mineral apposition fronts covering almost the entire bone surface. Reversal of photoperiod resulted in (i) rapid ovarian regression and loss of medullary bone in females previously exposed to long day conditions, and (ii) rapidly increased ovarian size and induction of medullary bone formation in females previously exposed to short days. These data demonstrate that the skeleton is exquisitely sensitive to photoperiod during avian seasonal reproduction and the central actions of thyroid hormone are essential for medullary bone formation. Elucidation of mechanisms that mobilise calcium and synchronise egg shell formation during the daily reproductive cycle may identify novel pathways that couple bone resorption and formation.

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OC6.2

Glucocorticoids activation by 11beta-hydroxysteroid dehydrogenase type 1 protects against inflammatory bone loss in a murine model of chronic inflammation

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Local and systemic bone loss is a common complication in patients with chronic inflammatory disease. Previously, we have identified that glucocorticoid (GC) activation by the enzyme 11beta-hydroxysteroid dehydrogenase type 1 (11β-HSD1) is increased within tissues such as bone during systemic inflammation. However, whilst effective at suppressing inflammation, in excess, GCs drive osteoporosis. To determine the contribution of 11β-HSD1 activated glucocorticoids to inflammatory bone loss, we crossed an 11β-HSD1 null mouse onto a transgenic murine model of chronic inflammation (TNF-Tg). The histology of tibia and bones of the hind paw were assessed by micro-Ct and in paraffin embedded sections. Bone strength was determined by three point bending. Serum markers of bone metabolism were assessed by ELISA and gene expression of osteoblast and osteoclasts determined by Real Time RT-PCR. Total osteoclast numbers within bone were determined by TRAP staining. At 9 weeks TNF-Tg/HSD1KO mice had greater juxta articular and systemic bone loss compared to TNF-Tg animals on a wild type background, with increased cortical bone erosions, decreased trabecular bone volume (decreased 70%; $P<0.0005$), decreased trabecular thickness (TNF-Tg, 66 μm vs TNF-Tg/HSD1KO 45.3 μm; $P<0.005$) and decreased trabecular number (decreased 68.2%; $P<0.005$). This was coupled with significantly reduced breaking points in TNF-Tg/HSD1KO mice relative to TNF-tg animals in three point bending tests. Serum markers of bone formation and gene expression of osteoblast markers were significantly decreased in the TNF-Tg/HSD1KO mouse (P1NP, Runx2 and osteoprotegerin reduced by 16%, 33% and 81% respectively; $P<0.05$). In contrast, serum markers of bone resorption and osteoclast numbers at sites of bone loss were significantly increased in both TNF-tg and TNF-Tg/HSD1KO mice relative to non-inflammatory controls. This study demonstrated that local glucocorticoids produced by 11β-HSD1 protect against inflammatory bone loss at sites of local joint destruction and systemically in this TNF-Tg model of chronic inflammation.

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OC6.3

Generation of *multiple endocrine neoplasia type 1* and *death-domain-associated protein* pluripotent stem cell lines to investigate mechanisms of pancreatic neuroendocrine tumourigenesis

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Background
Despite a wealth of gene-discovery studies identifying recurrently mutated genes in hereditary and sporadic endocrine tumours, the molecular mechanisms underpinning tumourigenesis frequently remain ill-defined, in part reflecting a lack of physiologically relevant model systems to investigate gene function. Here, using pancreatic neuroendocrine tumours as an example, we explored the utility of human induced pluripotent stem cell (iPSCs) and CRISPR/Cas9 gene-editing to investigate how inactivating mutations in *MEN1* and *DAXX* contribute to tumour formation.
Methods
20-nucleotide guide RNAs (gRNAs) were designed to target the coding-region of *MEN1* (exons 2/3) and *DAXX* (exon 3), and were cloned into a bicistronic Cas9/scaffold-RNA vector (with puromycin resistance selection cassette). The targeting efficiency of each gRNAs was evaluated following transfection in HEK293 and/or HeLa cells. ChIPS4 iPSCs were subsequently electroporated with validated *MEN1* or *DAXX* gRNA/Cas9 vectors and single-cell clonal populations established. Pluripotency markers were visualised by immunofluorescence, whilst *MEN1* and *DAXX* gene-targeting was assessed by western blot and DNA sequence analysis.
Results
gRNAs targeting *MEN1* and *DAXX* were functionally active in HEK293 and HeLa cells, resulting in mono-allelic or bi-allelic inactivating mutations at the respective genomic sites. Similar activity was observed in iPSCs with the generation of 6 mutant *MEN1* lines (3 mono-allelic, 3 bi-allelic) and 6 mutant *DAXX* lines (5 mono-allelic, 1 bi-allelic). When compared with wild-type iPSCs, *MEN1* mutant lines demonstrated no initial differences in cell morphology or pluripotency marker expression. However, after serial passage, colonies with bi-allelic *MEN1* inactivation underwent spontaneous differentiation with reduced proliferation. Similarly, although mono-allelic *DAXX* mutant cells were indistinguishable from wild-type iPSCs, bi-allelic *DAXX* inactivation resulted in cellular differentiation, reduced proliferation and a phenotype consistent with senescence.
Conclusions
CRISPR/Cas9 gene-editing provides an efficient tool to generate genetically-tractable stem cell models to investigate endocrine tumourigenesis. Here, we demonstrate that expression of Menin and DAXX is likely required for long-term maintenance of pluripotency.

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OC6.4

G-protein coupled oestrogen receptor mediates Hippo pathway signalling and survival outcomes in colorectal cancer patients

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Oestrogenic effects on colorectal cancer (CRC) incidence, proliferation, and patient survival remains controversial. We have previously shown enzymic pathways favouring oestradiol (E_2) synthesis are upregulated in CRC, and stimulation of the G-protein coupled oestrogen receptor (GPER) by E_2 increases CRC proliferation. Here we interrogated The Cancer Genome Atlas (TCGA) Colon Adenocarcinoma (COAD) database to determine all oestrogen metabolism enzymes and oestrogen receptors, and how expression effected patient survival. Furthermore, we hypothesised that the Hippo signalling pathway, an evolutionary conserved proliferative pathway regulated by GPER action, is mediated by E_2 in CRC. Using *in vitro* (proliferation assays, immunocytochemistry, immunoblotting) and *in vivo* (xenograft tumour) models, we examined how E_2 through GPER alters Hippo signalling, with a particular focus on Yes-associated protein (YAP), transcription coactivator with PDZ-binding motif (TAZ), and connective tissue growth factor (CTGF). The TCGA COAD dataset ($n=440$) showed CRC favours E_2 synthesis, supporting our previous findings. Further analysis revealed ERalpha, ERbeta, and GPER are all significantly ($P<0.0001$) downregulated in CRC compared to normal colon. However, GPER remains the most abundantly expressed oestrogen receptor. CRC patients with high tumour GPER expression ($n=110$) had a significantly ($P<0.05$) worse survival. In HCT116 and HT-29 CRC cell lines, stimulation of GPER with E_2 or G1, a specific GPER agonist, altered Hippo signalling by increasing YAP phosphorylation, and TAZ and CTGF expression. G15, a specific GPER antagonist, blocked these responses. Furthermore, G15 significantly ($P<0.01$) inhibited the *in vivo* growth of HCT116 tumour xenografts. Further TCGA COAD analysis showed CRC patients with high TAZ expression had significantly worse survival outcomes. Our data suggests a novel pathway through which E2-GPER signalling can mediate the Hippo pathway in CRC resulting in increased proliferation. The TCGA COAD dataset supports this hypothesis and suggests targeting GPER and/or Hippo signalling may provide therapeutic benefit to patients with CRC.

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OC6.5

Tumor immunosuppressive environment and tamoxifen resistance in rats exposed to EE2 *in utero* can be prevented with HDAC and DNMT inhibitors

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Maternal exposures during pregnancy to endocrine disrupting chemicals increase daughter's breast cancer risk in humans and animal models. We have previously found that these exposures also pre-program offspring's mammary tumors to exhibit increased resistance to antiestrogen therapy, and that treatment with valproic acid (HDAC inhibitor) and hydralazine (DNMT inhibitor) prevented antiestrogen resistance. Here we investigated if maternal exposure to ethinyl estradiol (EE_2) alters tumor immune environment in the offspring. Pregnant Sprague Dawley rats received 0 or 0.1 ppm EE_2 via diet during gestation days 10–20. Estrogen receptor positive (ER+) mammary tumors in the offspring were induced with 9,12-dimethylbenz[a]anthracene, and when a tumor reached 13 mm in diameter, offspring were treated with 15 mg/kg tamoxifen (TAM), with or without 1.2 g/kg valproic acid and 5 mg/kg hydralazine. Before TAM treatment, mammary tumors in the EE_2 offspring exhibited higher mRNA levels of *Foxp3* ($P=0.017$), *Tgfβ1* ($P=0.075$) and *PD-L1* ($P=0.013$) than tumors in the control offspring. TAM treatment further upregulated *Foxp3* ($P=0.01$) and *Tgfβ1* ($P<0.001$) as well as *PD-1* ($P<0.001$) in the EE_2 offspring (compared with no TAM treated EE_2 offspring). However, when *in utero* EE_2 exposed rats received both TAM and valproic acid+hydralazine, mRNA levels of *Foxp3* ($P<0.001$), *Tgfβ1* ($P=0.003$), *PD-L1* ($P=0.011$) and *PD-1* ($P<0.001$) were significantly lower than in the EE_2 offspring that were treated with TAM only. No changes were seen in the control offspring by TAM, with or without valproic acid+hydralazine treatment. Since elevated levels of Foxp3 and TGFβ1 are indicative of immunosuppression, and PD-L1 and its receptor PD-1 prevent cytotoxic T lymphocytes (CTLs) from killing cancer cells, our data suggest that *in utero* EE2 exposure promotes immunosuppressive tumor microenvironment that allows cancer cells to evade elimination by CTLs, and this effect is reversible by treatment with HDAC+DNMT inhibitors.

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OC6.6

Calcium-sensing receptor (CaSR) mutations in hypercalcaemic and hypocalcaemic patients cluster at the extracellular dimer interface

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Loss- and gain-of-function mutations of the calcium-sensing receptor (CaSR) cause familial hypocalciuric hypercalcaemia (FHH) and autosomal dominant hypocalcaemia (ADH), respectively. The CaSR is a homodimeric receptor that has a 612 amino acid extracellular domain (ECD), which binds extracellular calcium (Ca^{2+}_e) and mediates dimer interactions upon ligand binding. The ECD consists of lobes 1 and 2, and a cysteine-rich domain (CRD). To elucidate the structure-function relationships of the ECD, we examined the location of CaSR ECD mutations reported to date in FHH and ADH probands using recently established CaSR crystal structures. These studies identified that 121 FHH and 65 ADH mutations affected ECD residues, with >50% of FHH mutations and >75% of ADH mutations being located at the dimer interface. Mutations predicted to disrupt key CaSR dimer-dimer interactions included: a lobe 1 Tyr161Cys mutation, which impaired an interprotomer interaction with the lobe 1 Pro55 residue; a Ser171Asn mutation predicted to disrupt a lobe 2 interprotomer salt bridge, which forms upon agonist binding; and a Gly553Arg mutation, which altered interprotomer hydrophobic interactions within the CRD. We characterized the effect of these mutations on CaSR function in HEK293 cells following stimulation with Ca^{2+}_e, by measuring fold-change responses of nuclear factor of activated T-cells (NFAT), which is a downstream mediator of CaSR signaling. The Tyr161Cys, Ser171Asn and Gly553Arg dimer interface mutations were shown to markedly impair CaSR-mediated NFAT signalling. Indeed, cells expressing wild-type CaSR showed a >20-fold increase in NFAT responses following stimulation with 2.5 mM Ca^{2+}_e, compared to a <5-fold increase in NFAT responses for mutant CaSR-expressing cells ($P<0.01$, $N=4$ biological replicates). Thus, these studies demonstrate that the majority of FHH1- and ADH1-causing CaSR ECD mutations are located at the dimer interface, and predicted to alter CaSR function through effects on dimer formation or agonist-induced conformational changes that occur at the dimer interface.

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Poster Presentations

Adrenal and Steroids

P001

PAPS synthase 2 is the major PAPS-supplying enzyme for DHEA sulfation

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PAPS (3′-phospho-adenosine-5′-phosphosulfate) synthases provide the cofactor PAPS for all human sulfation pathways. The cytoplasmic sulfotransferase SULT2A1 uses PAPS mainly to sulfate the androgen precursor DHEA (dehydroepiandrosterone). Apparent SULT2A1 deficiency is caused by mutations in the gene coding for PAPSS2; suggesting some form of PAPS synthase-sulfotransferase pairing. Knockdown studies within human adrenocortical NCI-295R cells now show that PAPSS2 is required for efficient DHEA sulfation, while PAPSS1 appears to be dispensable. As recombinant proteins, both PAPS synthases have similar specific activities in their APS kinase domains that catalyze the rate-limiting step of overall PAPS biosynthesis. DHEA sulfation rates in cells are significantly higher when cytoplasmic SULT2A1 is co-expressed with cytoplasmic PAPSS2, than any other localization variant. Proximity ligation assays between SULT2A1 and PAPSS2, and to a lesser extend also with PAPSS1, indicate a protein-protein interaction. Computational docking of PAPS synthases revealed a binding site for SULT2A1 within the APS kinase domain of PAPSS2. Energy-dependent scoring of various docking solutions identified the PAPSS2-SULT2A1 complex as more stable than the corresponding PAPSS1 complex; this interaction was also specific compared to the closely related SULT2B1 protein. This extended functional module within a human sulfation pathway may provide a better understanding of clinically observed PAPSS2 mutations.

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P002

ARID1a, a SWI/SNF subunit, is important for the regulation of a subset of glucocorticoid responsive genes

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In the clinic, glucocorticoids are widely used due to their anti-inflammatory properties. Despite their huge benefits, prolonged use is often associated with severe side effects as well as the development of glucocorticoid resistance in some cases. Mutations in an important SWI/SNF subunit, ARID1a, have previously been linked to glucocorticoid resistance and are associated with a vast number of human cancers. Determining the functional role of ARID1a in glucocorticoid receptor (GR) signalling is therefore of great importance. Chromatin-remodelling by the SWI/SNF complex is crucial for genomic GR signalling, with chromatin accessibility being dynamically altered at GR binding sites in target genes to regulate transcription. We therefore initially hypothesized ARID1a to be a key regulator of GR mediated transcriptional regulation. This hypothesis was tested using RNA sequencing (RNA-SEQ) to determine the genome-wide effects of loss of ARID1a on glucocorticoid target gene expression in HeLa cells. We found that ARID1a siRNA knockdown had no impact upon RNA expression of the majority of robustly regulated glucocorticoid responsive genes. Instead, the data demonstrated the importance of glucocorticoid regulation on cell-cycle progression through ARID1a, revealing disruption of P53 pathways and a potential role in DNA repair mechanisms. As both GR and P53 directly interact with ARID1a, we tested the impact of loss of ARID1a upon protein interactions. Liquid chromatography mass spectrometry was used to identify GR interacting proteins. These proteomics studies have enabled us to assess how ARID1a knockdown alters components of the protein complex bound to GR at the DNA template. The proteomics data corroborates our RNA-SEQ data; again revealing a loss of GR association with p53 related and DNA repair proteins, thus supporting a novel role of GR in control of cell-cycle through interactions with ARID1a.

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P003

Intra-adrenal cytokine expression during inflammatory stress is immune-dependent

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The hypothalamic-pituitary-adrenal axis is the primary neuroendocrine system activated to establish homeostasis during the stress of critical illness and surgery. However, such critical states also trigger a systemic inflammatory activation that usually precedes the release of adrenocorticotrophic hormone (ACTH) and cortisol. Systemically or locally induced inflammation of the adrenal gland had been described during critical illness. This facilitates an immune-adrenal cross-talk that could modulate cortisol release in this condition.
We demonstrate that immortalised murine adrenocortical ATC7 cells do not show a significant activation of pro-inflammatory cytokines in response to inflammatory stress (lipopolysaccharide, LPS). There was no significant increase in the expression of both interleukin-6 mRNA and protein, and neither co-treatment with ACTH nor interferon gamma had any effect on interleukin-6 mRNA expression. Furthermore, there was no significant effect in the regulation of the key steroidogenic genes in response to these treatments. This led us to hypothesise that immune-effector cells might play a central role in the modulation of both the inflammatory and steroidogenic pathways within the adrenal cells. We therefore developed a novel trans-well co-incubation model of THP1 (human monocytic cell)-derived macrophages and ATC7 cells. We demonstrate a significant surge of IL-6 mRNA in ATC7 cells as a result of co-incubation with the THP1 cells, and this effect was potentiated by treatment with LPS. Furthermore, we also found significant changes in key steroidogenic enzymes (including StAR and DAX-1). Moreover, 24-hour co-incubation with glucocorticoid prevented, in a dose related manner, the IL6 mRNA increase induced by LPS stimulation.
Our co-incubation model suggests that the expression of inflammatory cytokines in adrenal cells is immune-dependent. Furthermore, glucocorticoids can regulate this immune-adrenal interaction with implications to clinical practice. More studies, aimed at the changes within the THP1 cells are needed to elucidate this interaction.

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P004

Development of a liquid chromatography tandem mass spectrometry assay for the profiling of salivary androgens and gestagens

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Measuring circulating androgen and gestagen concentrations is essential for the diagnosis and treatment monitoring of pathological conditions caused by abnormal steroidogenesis, such as congenital adrenal hyperplasia (CAH) and polycystic ovary syndrome (PCOS). Saliva collection represents a simple and non-invasive technique advantageous for multi sample profiling. We therefore developed a liquid chromatography-tandem mass spectrometry assay for the simultaneous quantification of progesterone, 17-hydroxyprogesterone, classic pathway androgens (testosterone, androstenedione) and 11-oxygenated pathway androgens (11-hydroxyandrostenedione, 11-ketotestosterone). 11-oxygenated androgens have recently been show to represent the major androgens in CAH and PCOS and 11-ketotestosterone activates the androgen receptor with similar potency to testosterone. Samples (300 μL) were prepared by supported liquid extraction with dichloromethane. Online automated solid phase extraction (Waters OSM) of the reconstituted extracts was performed using C18-cartridges prior to LC on a C8-column with a water/methanol gradient. Quantification was performed with a Waters TQ-S mass spectrometer. Total run-time injection-to-injection was 6.4 minutes. The assay was validated for sensitivity, specificity, recovery, matrix effects, intra- and interassay imprecision, post-extraction stability, carry-over and dilution linearity. All parameters were acceptable according to the FDA Guidance for Industry: Bioanalytical Method Validation. Applicability of the assay was demonstrated by determining diurnal and menstrual alterations for three healthy female volunteers.

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P005

20β-Dihydrocortisol; a weak endogenous agonist of the glucocorticoid receptor but a potent agonist of the mineralocorticoid receptor

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Cortisol conversion to 20β-dihydrocortisol (20β-DHF) has been reported in many tissues and cells, including skin, muscle, thrombocytes and fibroblasts, although the enzyme responsible is poorly characterised. We have attributed 20β-DHF generation to carbonyl reductase 1 and shown increased activity of this pathway in adipose tissue in obesity in humans, horses and mice. This study addressed the hypothesis that 20β-DHF activates glucocorticoid receptors (GR) and mineralocorticoid receptors (MR).

Docking calculations were conducted to compare binding interactions formed by cortisol and 20β-DHF with the GR and MR ligand binding pockets. The ligands showed similar predicted interaction patterns with both receptors. However, the 20β-hydroxyl group of 20β-DHF seemed to be tolerated better tolerated by MR to retain activation than by GR. Using HEK293 cells transfected with GR or MR and a MMTV-luciferase reporter we compared receptor activation in the presence of increasing concentrations of cortisol or 20β-DHF (100 nM- 5 μM for 6 hours). We demonstrated that 20β-DHF induced significant activation of GR but only at much higher concentrations than cortisol (cortisol 100 nM: 2.6 ± 0.4 fold induction compared with vehicle, 20β-DHF 2.5 μM; 1.8 ± 0.2 fold induction, $P<0.005$ compared with vehicle). In contrast 20β-DHF induced MR activation equivalent to that of cortisol at much lower concentrations (cortisol 100 nM; 2.9 ± 0.3 fold induction, 20β-DHF 100 nM; 2.4 ± 0.2 fold induction, $P<0.005$ compared with vehicle). A Microarray Assay for Real-time Co-regulator-Nuclear Receptor Interaction (MARCoNI) of 20β-DHF as a GR or MR ligand supported these findings. On binding 20β-DHF GR recruited only 36% of co-regulators recruited by cortisol while MR recruited 77% of the co-regulators recruited by cortisol.

In conclusion, we have demonstrated that 20β-DHF is a weak endogenous GR agonist but a potent MR agonist. Increased production of 20β-DHF in obesity may contribute to dysregulation of glucocorticoid signalling with complex and likely tissue-specific consequences.

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P006

Improving the therapeutic index of topical anti-inflammatory steroids: angiostatic effects of 5α-tetrahydrocorticosterone vs hydrocortisone

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Glucocorticoids (GC) have potent anti-inflammatory effects, acting mainly through the glucocorticoid receptor (GR). However GCs have debilitating side effects and a safer alternative is required. 5α-tetrahydrocorticosterone (5αTHB, a metabolite of the natural rodent glucocorticoid corticosterone) may provide a solution: 5αTHB is anti-inflammatory *in vivo*, effective topically to suppress irritant dermatitis, but with fewer systemic adverse effects. Topical GCs have additional local side effects, in particular impaired wound healing, which occurs largely due to the inhibition of angiogenesis. Here it was hypothesised that 5αTHB suppresses angiogenesis less than hydrocortisone, a commonly prescribed topical therapeutic GC.

Angiogenesis was studied using an *ex vivo* model. Mouse (C57Bl6, male, 8–10 weeks) aortas were isolated, divided into rings (1 mm) and cultured in collagen gel with foetal calf serum and vascular endothelial growth factor to stimulate vessel outgrowth formation. The number of vessel outgrowths was counted after 7 days incubation with steroid or vehicle control (1 nM-10 μM, $n=8$/dose) to determine whether the steroids inhibited new vessel formation. Transcripts of genes involved in GC responsive pathways were quantified in rings exposed to hydrocortisone (1μM) or 5αTHB (3 μM), using qPCR. Data are mean+/−SEM; $^*P<0.05$; vs control.

Vessel outgrowth was suppressed by both hydrocortisone (to 29%* control, 1μM, EC_{50} 867 nM) and 5αTHB (to 30%* control, 3 μM, EC_{50} 2399 nM) in a concentration dependent manner. Hydrocortisone modulated expression of inflammatory mediators and extracellular matrix remodelling genes in aortas. Compared to control *Cxcl5* was lower (31%* control), *Dusp1* higher (200%* control), *Col4a1* higher (190%* control) and *Mmp9* lower (16%* control) after hydrocortisone treatment. 5αTHB however had more limited effects, only decreasing abundance of *Pecam1* mRNA (to 63%* control).

In conclusion, 5αTHB suppressed angiogenesis less than hydrocortisone, and in addition, exerted its actions on the aorta differently. This knowledge will help us to assess 5αTHB's potential as a safer topical anti-inflammatory treatment.

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P007

Salivary cortisol response to the short Synacthen® test provides a reliable alternative to serum measurement in the assessment of suspected hypoadrenalism

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Background

Serum total cortisol responses to the short Synacthen® test (SST) are used to confirm or refute a diagnosis of adrenal insufficiency. Salivary cortisol measurement offers a non-invasive alternative and has the potential advantage of evaluating free, bioavailable cortisol. However, reference ranges and its performance in the investigation of suspected hypoadrenalism (SH) have not been firmly established.

Aims

1. To establish the salivary cortisol response to SST in healthy volunteers (HV), patients with low protein concentration (secondary to nephrotic syndrome or liver cirrhosis; NS-C) and women taking an oestrogen-containing oral contraceptive pill (OCP).
2. To evaluate the performance of a lower reference limit (LRL) determined in HVs in patients with SH.

Methods

An SST was undertaken in 139 HVs, 29 patients with SH, 24 OCP-females and 10 NS-C patients. Salivary cortisol was measured using an in-house liquid chromatography-tandem mass spectrometry assay. The mean and LRL (mean-1.96SD) of the salivary cortisol response to Synacthen® were derived from log-transformed concentrations; the LRL was applied as a diagnostic cut-off in SH patients.

Results

The 30-minute salivary cortisol response to SST in HVs showed a non-Gaussian distribution, with no significant gender difference. Concentrations ranged between 10.1 and 39.7 nmol/L, with mean concentration 19.3 nmol/L and LRL 10.3 nmol/L. Mean concentrations in OCP-females (19.7 nmol/L) and NS-C patients (19.0 nmol/L) were not different from HVs ($P=0.69$ & $P=0.75$, respectively). The LRL correctly identified all patients with hypoadrenalism (7/7) and incorrectly diagnosed hypoadrenalism in 4/22 unaffected patients.

Conclusions

This study provides a reference range and estimated LRL for the salivary cortisol response to Synacthen® in healthy volunteers. The LRL has 100% sensitivity and 82% specificity when applied as a cut-off in patients with suspected hypoadrenalism. Salivary cortisol responses to the SST may offer an alternative to serum measurement and may be especially useful in patients with altered protein states, although assay-specific reference ranges are needed.

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P008

Is renin a useful marker of mineralocorticoid replacement in addison's disease?

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The utility of renin measurement in guiding mineralocorticoid replacement is unclear. To address this we retrospectively examined the parameters and treatment of 97 patients with Addison's disease over a five year period.

Methods

Adrenal replacement, blood pressure (BP), orthostatic BP response, urea, sodium, potassium and renin levels of 97 patients attending our clinic were collected over the period 2012–2016. Data were analysed in R version 3.3.2.

Results
97 patients attending for 397 appointments were reviewed. Renin level was measured on 227 (57%) of attendances, 68% were elevated (>45mU/L) with 48% above 90 mu/L. A modest but significant negative association with plasma sodium ($P<0.001$, R^2 0.189) and a significant but weak association with potassium ($P<0.001$. R^2 0.062) and urea ($P<0.001$, R^2 0.053) were noted. There was no association with systolic or diastolic BP or orthostatic response. A renin level >90 mu/L was 64% sensitive and 28% specific for detecting another feature of mineralocorticoid deficiency (hyponatraemia, hyperkalaemia, postural drop). A renin level >45 ml/l was 79% specific but only 24% sensitive. Measurement of renin was more likely to stimulate an adjustment in fludrocortisone dose (chi^2 $P=0.019$) however, patients with a deranged renin level were as likely to have a dose change as those with a normal renin level (5–45 mU/L, chi^2 $P=0.454$). Of the 77 patients with renin levels greater than twice the upper limit of normal, a dose increase occurred in only 23 patients (29%), in 17 of whom, sodium, potassium and postural BP were unremarkable.
Conclusion.
Our study suggests that although renin level does have important clinical correlates with serum biochemistry, high renin levels have only modest sensitivity and low specificity for detecting other features of mineralocorticoid deficiency. This is reflected in a high variability in therapeutic response to deranged renin levels and the role of renin in guiding management of patients with Addison's disease remains undefined.

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P009

Using mouse adrenocortical cell lines to investigate how glucocorticoid synthesis is dynamically regulated

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Glucocorticoid hormones (cortisol in man, corticosterone in rodent; CORT) are vital for maintaining normal homeostasis in multiple systems ((e.g., the cardiovascular, metabolic, and immune systems), and for an optimal response to acute and chronic stress. Plasma CORT is released from the adrenal zona fasciculata (ZF) in response to circulating levels of pituitary-derived adrenocorticotropin hormone (ACTH). ACTH binds to the MC2-receptor on the membrane of ZF cells and rapidly stimulates *de novo* biosynthesis of CORT by activating cAMP/PKA/CREB-mediated transcription of steroidogenic proteins and in turn CORT synthesis. The release of ACTH and CORT is governed by an ultradian rhythm (in the rat: hourly pulses of hormone over a 24hr-cycle). Our current *in vivo* studies indicate that phosphorylation and synthesis of the steroidogenic proteins in the rat adrenal are also subject to an ultradian rhythm. To help understand how the body translates the ultradian rhythm of ACTH stimulation to the adrenal gland, we have been studying steroidogenic pathways in the recently developed (and long-awaited) mouse ZF-ATC7 cell line. We have found that hourly pulses of 10 nM ACTH are able to stimulate CREB-phosphorylation (pCREB) and steroidogenic gene transcription in ATC7 cells in the same dynamic manner to that observed *in vivo*. In contrast, when the same dose of ACTH is applied as a constant stimulus, the pCREB and steroidogenic gene transcriptional response is prolonged and exaggerated. In addition, when a large stress-dose of ACTH (100 nM) is applied after these treatment regimes, a significant increase in pCREB is only achieved in cells that have been exposed to pulsatile, rather than constant, ACTH. Together this supports our *in vivo* observations that pulsatile ACTH is important for the optimal responsiveness of the adrenal, and that ATC7 cells are a suitable tool to investigate the regulation of CORT ultradian rhythm *in vitro*.

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P010

The impact of a point-of-care rapid cortisol assay on success rate, procedural efficiency and radiation dose in adrenal vein sampling for primary hyperaldosteronism

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Introduction
Catheterisation of the right adrenal vein when performing adrenal vein sampling (AVS) is challenging. The AVS Accuracy Kit (AAK) (Trust Medical, Kasai, Japan) enables point-of-care confirmation of accuracy of AVS by rapid cortisol assay. We investigated whether use of AAK during AVS would impact upon procedural success, number of venous samples taken, radiation dose and screening time.
Methods
0.5 ml of each venous blood sample was centrifuged immediately and 0.1 ml of plasma applied to the AAK test strip and read at 3 min within the interventional radiology suite. A prospective series of 10 consecutive patients (single operator) undergoing AVS using AAK (AAK group) was compared to a retrospective series of 40 consecutive patients without AAK (nAKK group). We recorded procedural success (adrenal/peripheral cortisol ratio>2), number of venous samples taken, screening time and radiation dose.
Results
At first procedure, right AVS was technically successful in 32/40(80%) in the nAAK group compared to 9/10(90%) in the AAK group. Subsequent successful repeat procedures (separate occasion) were performed in 4 patients leading to a combined success rate in the nAAK group of 90% (36/40). Point-of-care cortisol estimations corroborated with laboratory cortisol measurements by immunoassay thus confirming accuracy. There were non-significant differences between groups in the number of venous samples and screening time per procedure (table). There was a significant reduction in the radiation dose-area-product per patient in the AAK group (table 1).

Table 1 Comparison between groups. Parametric data shown as mean (±S.D.) and non-parametric as median (IQR).

Measurement	nAAK group	AAK group	*P*
Age (years)	56 (±13)	52 (±13)	0.39
Successful catherisation at first procedure (%)	32/40 (80%)	9/10 (90%)	0.60
Number of right-sided venous samples per case (min–max)	2 (1–7)	2.5 (1–5)	0.62
Number of left-sided venous samples per case (min–max)	1 (1–3)	1 (1–3)	0.85
Radiation dose (μGym2)	5383 (1944–9629)	2107 (1598–4068)	0.03
Screening time (minutes)	12.1 (7.1–20.4)	6.8 (4.3–17.6)	0.12

Conclusion
The AAK can reduce the screening time and radiation dose during AVS. It may improve procedure success and reduce the need for repeat procedures although further confirmatory studies are needed.

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P011

Does cortisol exposure from the Hydrocortisone day curve predict mortality, type II Diabetes or lipid profiles?

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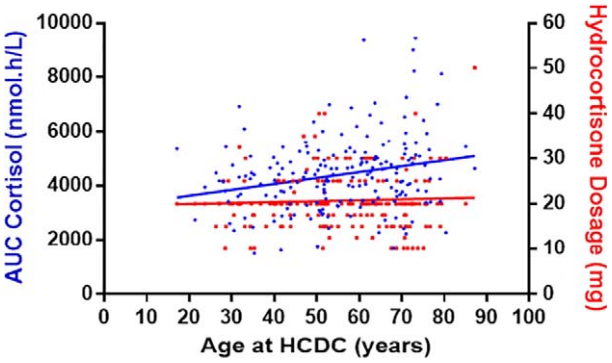
Background
Hydrocortisone day curves (HCDCs) are commonly used to assess hydrocortisone replacement for patients with adrenal insufficiency (AI).
Methods
HCDCs were obtained for 216 adrenally insufficient patients between 2004 and 2012 at Imperial College Healthcare NHS Trust. The area under the curve (AUC) was calculated for each patient's day profile. Lipid profiles and glycated haemoglobin (HbA1c) values were recorded for each patient at both the time of the HCDC and after 5 years.
Results
The highest AUC tertile group were significantly older than the other groups ($P<0.01$). There was a significant positive correlation between the AUC cortisol and the age at the time of the HCDC ($r(s)=0.22$, $P=0.001$), but no significant

correlation between age and the cumulative hydrocortisone dose ($r(s) = -0.02$, $P = 0.73$). This suggests that we prescribe the same dose of hydrocortisone regardless of age, but these same doses achieve different AUCs depending on age. The group with the highest AUC cortisol had the poorest survival outcomes, with a 79.4% survival rate after five years (compared to 96.8% in the lowest AUC tertile ($P < 0.01$). The HbA1c taken after five years did not significantly correlate with the AUC cortisol. ($r(s) = -0.08$, $P = 0.45$, $n = 88$). There was also no significant correlation between the AUC cortisol and total serum cholesterol at baseline ($r(s) = 0.12$, $P = 0.26$, $n = 93$) or after 5 years ($r(s) = -0.17$, $P = 0.11$, $n = 92$).



Conclusions
This study found that older patients have higher AUC cortisol values. There was also no significant correlation between age and the hydrocortisone dose, which suggests that the higher cortisol exposure must be caused by a decline in the rate of cortisol metabolism and urinary excretion. The AUC cortisol was not associated with increased HbA1c levels or poorer lipid profiles, at baseline or after five years. A longer follow-up period is needed to fully assess the effect of increased cortisol exposure.

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P012

It's a matter of time: the emergence of autoimmune polyendocrine syndrome in autoimmune Addison's disease reaches 100% among those diagnosed more than 50 years ago

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Addison's disease (AD) has an estimated prevalence of 126–144 per million among Northern European populations. Average age at diagnosis is 39, but AD may be diagnosed from pre-teens to 80 year olds.
AD may occur in isolation or as part of autoimmune polyendocrine syndromes. Previous studies identified significant associations with autoimmune thyroid disease (predominantly hypothyroidism), type 1 diabetes mellitis, vitiligo, vitamin B12 deficiency and coeliac disease.
We examined self-reported rates of associated endocrine and autoimmune conditions among British Autoimmune Addison's Disease (AAD) patients, all members of the Addison's Disease Self-Help Group ($n = 444$). Co-conditions were analysed by years since diagnosis, with a range from 50 years post-diagnosis. The average years since diagnosis was 12.2. Cohort sizes for advancing decades post-diagnosis were small, making significance tests problematic. Rates of associated conditions generally increased over time, although smaller cohorts were not consistently progressive.
Thyroid conditions increased steadily among each post-diagnosis cohort, to reach 100% of those diagnosed >50 years ago. Type 1 diabetes peaked at 26% among the 31–40 year cohort. Coeliac disease, vitamin B12 deficiency and vitiligo peaked at 10%, 20% and 30% respectively among those diagnosed 41–49 years ago. Premature ovarian/testicular failure peaked at 20% of those diagnosed >50 years ago. (See chart).
Larger Swedish and German studies found broadly similar proportions of AAD patients with thyroid disease. Both had higher rates of insulin-dependent diabetes; rates of B12 deficiency in Sweden were also significantly higher.

These findings are a reminder that AAD patients require lifelong monitoring for the development of co-conditions. Endocrinologists should assume that AAD patients are likely to develop a thyroid condition at some stage, and that AAD should be managed as potentially an autoimmune polyendocrine syndrome, even when it is diagnosed in isolation.

Table 1

Condition	Britain ($n = 444$)	Sweden ($n = 1305$)	Germany ($n = 2715$)	*P* value UK-Sweden
Thyroid	48%	47%	55%	0.666
T1Diabetes	6%	14%	8%	1
B12 deficiency	9%	18%	–	1

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P013

Short synacthen test requests may be reduced by considering test indication and identifying a 9am cortisol value that predicts test result

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Background
Short synacthen tests (SSTs) are routinely performed for the investigation of adrenal insufficiency (AI), but are costly and time consuming. The frequency of SST testing could be reduced by prioritising testing for specific indications (based on likelihood of failure of the test), and also by identification of an assay-specific 9am cortisol level that obviates the need to proceed to SST.
Methods
Retrospective review of indications and results of all SSTs performed over one year at our institution. Receiver-operating characteristic (ROC) curve analysis was performed based on the baseline serum cortisol level to obtain a predictive cut-off value. Cortisol was assayed by Centaur immunoassay (Siemens).
Results
450 SSTs were performed in one year. Failure rates varied according to indication; only 2% of patients failed SSTs if indicated for fatigue/malaise; substantially more patients failed for other indications such as following adrenal surgery (54%), suspected HPA axis suppression (57%), or reassessment of known HPA axis suppression (67%).
ROC curve analysis identified that a 9am cortisol of <56 nmol/L predicted failure with 100% sensitivity and >374 nmol/L provided 100% specificity to pass the test; for 99% sensitivity and specificity the values were 114 and 362 nmol/L respectively.
Conclusion
Pass rates for SSTs varied considerably depending on indication. The low failure rate for those with fatigue suggests that the test should only be performed if additional clinical parameters support the diagnosis of AI. A baseline serum cortisol level of <56 nmol/L predicted SST failure in all individuals; levels >374 nmol/L predicted a 100% pass rate. If SSTs were avoided in all individuals with a 9am cortisol outside these cutoffs, 154 tests would have been avoided, resulting in significant cost benefit.

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P014

Enteric coating delays the absorption of prednisolone variably and should not be used

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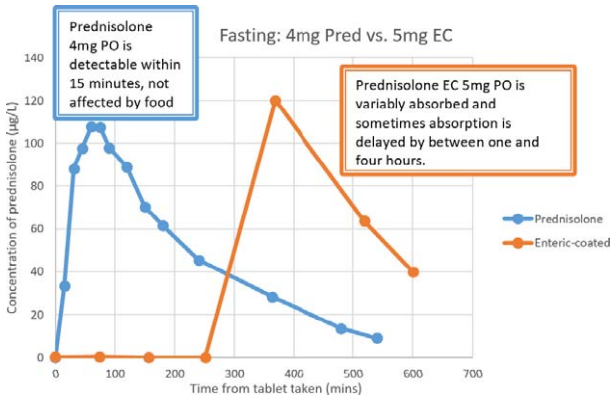
Once daily oral prednisolone has been shown to mimic the normal circadian rhythm better than other glucocorticoids. Our advice is to take prednisolone first

thing on waking and before breakfast to try to mimic the normal circadian rhythm as closely as possible. The leaflet that comes with prednisolone suggests that it should be taken with food. Enteric-coated prednisolone (EC) is believed to be kinder on the stomach, but there is no evidence for its use. We compared EC with standard prednisolone. Healthy volunteers were administered single doses of either 4 mg standard prednisolone or 5 mg EC in the morning.
Results
Standard prednisolone was reliably absorbed and detectable in the blood within 15 min with a mean time to maximal prednisolone concentration (T_{max}) of 55 min and a mean concentration at maximum (C_{max}) of 120.1 µg/l. EC showed considerable intra-individual variability in T_{max} and C_{max}. The rise in prednisolone concentration was delayed between one and four hours when EC was used, and in some volunteers, was not absorbed at all. Food had no effect on standard prednisolone absorption, but significantly delayed EC further. An example of the prednisolone profiles from one of the volunteers is shown.



An early peak in prednisolone levels is required to mimic normal circadian physiology. Because the enteric coating delays this variably, we would recommend that EC prednisolone is avoided when prednisolone is used as a replacement for primary adrenal insufficiency. A reliable and early peak is seen in patients and volunteers who take a single dose of standard prednisolone once daily, and we recommend that prednisolone replacement is taken first thing on waking.

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P015

How relevant is aldosterone and cortisol co-secretion?

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Background
Studies suggest that glucocorticoid hypersecretion alongside primary hyperaldosteronism (PA) is common and may contribute to the adverse metabolic phenotype. Adrenal crisis post-surgery for PA is rare.
Aim
To determine the prevalence of cortisol co-secretion in PA in patients at Imperial College London NHS Trust, Hammersmith Hospital (a tertiary referral centre for adrenal tumours).
Methods
Amongst patients who had undergone adrenal vein sampling for therapeutic stratification of PA over the past 5 years, 27 also had formal (overnight dexamethasone suppression) testing for hypercortisolism with overnight or low dose dexamethasone suppression test.
Results
Six patients were diagnosed as co-secretors (post dex cortisol range 75–435 nM) suggesting a prevalence of 22%. We describe their clinical history. Four co-secretors underwent unilateral adrenalectomy. Post-operatively, two failed a synacthen test (peak cortisol range 320-421) and one had a morning cortisol of 20 nmol/L. They were given glucocorticoid cover post-operatively but it is not known whether this was of benefit. Previously, no patients were given glucocorticoid cover, and there was no incidence of severe adrenal crisis post unilateral adrenalectomy for PA. No improvement in metabolic profile was seen in follow-up, except for the anticipated improvements in BP control.
Discussion
It is not clear whether co-secretion in PA is clinically relevant. The patients described here may not be entirely representative, since we have only recently prospectively assessed all PA patients for co-secretion. However we did not find differences in the metabolic profile at presentation between co-secretors and non-co-secretors. Perhaps co-secreting patients present earlier, and the burden of cortisol excess has not yet caused a dysmetabolic profile. In conclusion cortisol co-secretion in PA is more common than previously thought. Further studies are required to understand exactly what postoperative monitoring is required in this condition.

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P016

The potential use of I-131 Norcholesterol scan for large adrenal mass

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Background
Characterisation of large adrenal lesion is challenging. There is no single robust imaging marker in defining benignity, especially for lesions which are greater than 4cm and are believed to carry increased risk of malignancy.
A radiolabelled cholesterol analog tracer, I-131-Norcholesterol (NP-59), localises to adrenal cortical lesions. It has an established role in Conn's syndrome. It is not expected to concentrate in adrenocortical cancer. We aim to assess whether a combination of FDG PET-CT and NP-59 scan could be useful to define benignity of large adrenal lesions.
Methodology
We retrospectively reviewed cases referred to the adrenal service at University College London Hospital over the last six years. Patients with large adrenal mass were included when both FDG PET-CT and NP-59 studies had been undertaken and surgery was subsequently performed. Adrenal uptake of FDG was classified as concerning if the SUV was higher than liver activity. NP-59 study was classed as concerning if there is no concentration of the tracer in the lesion (i.e. higher uptake in the contralateral gland). Histology of the resected adrenal lesion was taken as the gold standard to define benignity.
Results
A total of ten patients were included. All adrenalectomy samples were confirmed to be benign (nine adenomas and one benign cyst). Eight patients had sub-clinical Cushing's syndrome pre-operatively. Average size of the lesion was 45 mm. Three lesions had unenhanced CT density of >10 HU and high FDG uptake. Two lesions had low CT density but high FDG uptake. All proven adenomas had high NP59 concentration on the concerning adrenal gland. The benign cyst has fluid CT density and low uptake on both FDG and NP59.
Conclusion
Our results confirm previous observation that NP-59 could be useful to confirm benignity of large adrenal lesions. A larger patient group including adrenocortical cancer would be needed to confirm this.

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P018

Prednisolone should be first line replacement therapy for adrenal insufficiency

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Introduction
We offer patients needing glucocorticoid replacement in primary and secondary adrenal insufficiency the choice of either once daily prednisolone or thrice daily hydrocortisone. A recent European study found no difference between prednisolone and hydrocortisone users in several markers, including glucose, weight, body mass index (BMI), systolic and diastolic blood pressure and waist circumference, although they did suggest an increase in cholesterol and low density lipoprotein (LDL) in a subgroup of these patients.
Method
Data from 79 patients on hydrocortisone and 62 patients on prednisolone for adrenal insufficiency attending Imperial College Healthcare NHS Trust was collected.
Results

	Hydrocortisone ($n=79$)	Prednisolone ($n=62$)	*P*-value
Dose (mg)	20.44 (6.40)	3.60 (1.04)	<0.0001
SBP (mmHg)	128.5 (18.8)	127.0 (18.4)	0.64
DBP (mmHg)	78.9 (11.20)	77.3 (8.8)	0.36
Waist circumference (cm)	100.8 (19.33)	97.6 (13.2)	0.30
Hip circumference (cm)	107.2 (15.42)	106.1 (11.19)	0.67
Weight (kg)	79.9 (17.5)	79.8 (15.6)	0.95
Height (m)	1.66 (0.09)	1.68 (0.12)	0.40
HbA1c (mmol/mol)	43.6 (15.5)	40.8 (11.5)	0.26
Total Cholesterol (mmol/l)	5.09 (1.28)	4.76 (1.07)	0.12
HDL (mmol/l)	1.42 (0.43)	1.33 (0.36)	0.24
LDL (mmol/l)	2.83 (1.02)	2.75 (0.91)	0.66
Glucose (mmol/l)	6.66 (3.20)	5.90 (3.04)	0.18
BMI kg/m^2	28.97 (6.33)	28.49 (5.35)	0.64
Waist hip ratio	0.94 (0.10)	0.92 (0.07)	0.31

Mean (SD), hydrocortisone v/s prednisolone.

In contrast to the other European study (1), we found that there was no significant difference in total cholesterol and LDL levels between hydrocortisone and prednisolone patients. There was no difference in any other risk factors.
Conclusions
Prednisolone once daily is more convenient than hydrocortisone thrice daily, and there is no difference in all the markers of cardiovascular risk measured. Because prednisolone mimics the circadian rhythm better than other glucocorticoids, it should be the first line therapy for adrenal insufficiency.

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P019

Does higher cortisol exposure during hydrocortisone replacement therapy lead to osteoporosis?

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Background
Glucocorticoid-induced osteoporosis is one of the major clinical concerns of long-term steroid treatment. Previous studies have shown that immunosuppressive doses of glucocorticoid can lead to osteoporosis. This study investigated whether there is a relationship between cortisol exposure and the development of osteoporosis in patients receiving replacement doses.
Methods
Hydrocortisone day curves (HCDCs) performed at Imperial College Healthcare NHS Trust between 2004 and 2012 were analysed. The area under the curve (AUC) cortisol was calculated for each patient's day profile and dual-energy X-ray absorptiometry (DEXA) scans were obtained from PACS imaging system, both at the time of HCDC and after five years for each patient. The change in mean bone mineral density (BMD), *T*-score and *Z*-score in the L2–L4 segment over five years was recorded ($n=24$, 16 females, 8 males).
Results
The mean age of the patients was 56.6 years (95% CI 51.2-62.01). The AUC cortisol did not significantly correlate with the baseline mean BMD ($r=-0.25$, $P=0.23$), *T*-score ($r=-0.21$, 0.33) or the *Z*-score ($r=0.05$, $P=0.83$) in the L2–L4 segment. This study found no significant correlation between the AUC cortisol and the change in mean BMD of the L2-L4 segment ($r=-0.12$, $P=0.56$), the change in *T*-score ($r=-0.16$, $P=0.44$) or the change in *Z*-score ($r=-0.31$, $P=0.15$) score in the L2–L4 segment over five years.
Conclusion
This pilot study has found no association between replacement cortisol exposure and mean BMD in patients receiving long-term steroid replacement although there may be a true relationship between higher cortisol exposure and the development of osteoporosis. It is known that decreasing the hydrocortisone dose decreases osteocalcin so it is necessary to investigate whether higher cortisol exposure disproportionately affects bone architecture compared to BMD.

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P020

How accurate are urinary metanephrines in screening for phaeochromocytoma?

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The Endocrine Society recommends urinary or plasma metanephrines as first choice screening tests for phaeochromocytoma due to their high sensitivity. Test specificity is limited by the influence of many commonly prescribed medications resulting in false positive results and additional investigations. The aims of this retrospective study were to (1) Determine the diagnostic accuracy of urinary metanephrines using current cut-off values and (2) Evaluate if alternative diagnostic thresholds would improve test performance.
Patients who underwent a clonidine suppression test, or had confirmed phaeochromocytoma on histology or imaging were included. All pre-operative urinary metanephrine (MAO) and normetanephrine (NMAO) results were obtained. 168 cases were identified (148 normal, 18 phaeochromocytoma (11 NMAO raised, 7 NMAO + MAO raised). In those with no phaeochromocytoma, MAO was elevated in 15.5% and NMAO in 57.4%. 119 (71.7%) were known to be taking interfering medications. Sensitivity + specificity for MAO at the upper level of normal (ULN) and two-fold elevation beyond ULN were 100% + 84.8% and 100% and 97.9% respectively. Sensitivity + specificity for NMAO at ULN and two-fold elevation beyond ULN were 100% + 41.8% and 66.7% + 95.2% respectively. ROC curve analysis of NMAO results (Area under curve- 0.908 ($P<0.001$)) identified an alternative higher cut-off with sensitivity + specificity 100% + 62.3% respectively.
Our data demonstrate excellent diagnostic accuracy of MAO using our current reference range but less accuracy in the more commonly elevated NMAO. Application of a higher diagnostic threshold will help reduce excessive investigation attributed to false positive results.

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P021

Clinical implications of the short synacthen test: an audit of its rational use in the assessment of adrenocortical insufficiency

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Aims
The short synacthen test (SST) is considered as the gold standard test to assess the viability of the hypothalamic-pituitary-adrenal axis. This study explores the appropriateness of its clinical use in a district general hospital. Furthermore, it assesses the effectiveness of the alternate use of 9AM cortisol in excluding hypoadrenalism and the cost-effectiveness of sampling both 30 and 60 minutes serum cortisol in SST.
Methods
All 222 SST's performed between 1/8/2015 and 31/07/2016 were evaluated retrospectively for pre-test probability of hypoadrenalism and timing of the test. Based on previous validation studies, a 9AM cortisol of >400 nmol/L and 30-min SST cut-off of >550 nmol/L (Roche-Gen-I assay) was considered indicative of adrenocortical sufficiency. Statistical correlations were obtained between various cortisol indices.
Results
Overall, 12% ($n=27$) of SST's were positive; 4% ($n=5$) in low and 21% ($n=22$) in high probability patients. Highly significant correlations between 0, 30 and 60min cortisols were observed ($P<0.001$; $R^2>0.450$). Furthermore, the correlation between 9AM cortisol and abnormal SST was highly significant ($P=0.005$; $R^2$0.615)
Discussion
This study showed majority of the SSTs performed could be avoided and replaced with the 9AM cortisol which has good predictive diagnostic utility. It also showed that the three-point SST (using 0, 30, 60 min cortisol) does not confer any added advantage over two-point SST (0 & 30 min cortisol). Implementation of these recommendations could result in annual cost savings of nearly £15000.

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P022

The effect of 4,4′ DDT, 4,4′ DDE, 4,4′ DDD, and 2,4′ DDD on dihydrotestosterone binding to and releasing from the androgen receptor

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The androgen receptor (AR) is required for the development of the male phenotype and traits. Some compounds, including diphenylethers and diphenylamines, inhibit AR activity by binding to a surface cleft named binding function 3 (BF-3). Such inhibitors bind by hydrophobic interactions between the two phenyl groups and the BF-3 site. A similar diphenyl group structure is found in 4,4′ DDT, 4,4′ DDE, 4,4′ DDD, and 2,4′ DDD, which have a diphenylethane or diphenylethylene scaffold. The effect of DDT and related compounds on tritiated dihydrotestosterone (^{3}H-DHT) binding to the AR ligand binding domain (LBD) was measured using a filter binding assay. Results showed that DDT and related compounds inhibited DHT from binding to the AR LBD with IC_{50} values ranging from 2 to 10 uM, under these conditions. Further analysis showed that DDT and related compounds induce the release of bound DHT from the AR LBD, with IC_{50} values ranging from 54 to 82 uM. These results suggest that DDT and related compounds may act as endocrine disrupting chemicals and allosterically regulate AR activity by binding to the BF-3 site and blocking binding of the steroid to the ligand binding domain.

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P023

Quality of life in patients with adrenal disease: a systematic review

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Evaluating patients with adrenal disease is uniquely challenging as biochemical parameters for assessing disease control or adequacy of hormone replacement are imprecise or lacking. QOL measures are increasingly being used to assess patients with adrenal disease, using a range of generic and disease specific measures. Reduced quality of life has been observed in patients with adrenal disease, even when biochemical cure is possible. We performed a systematic review of studies where QOL measures were used to evaluate adults with adrenal disease. The objectives were to describe how QOL has been defined and measured in relation to patients with adrenal disease, to critically appraise the use of QOL measures in this setting, and discuss the clinical implications of these findings. To our knowledge, this is the first systematic review of QOL in patients with adrenal disease. A total of 114 studies were included in the qualitative synthesis. QOL measures were a primary endpoint in 87%. They were used to evaluate interventions (such as glucocorticoid replacement strategies), assess long-term outcome, explore patient viewpoints, and identifying clinical or biochemical correlates. The majority of studies used quantitative methods, with generic SF-36 was the most frequently used measure. However disease specific tools (AddiQOL, CushingsQOL) are increasingly being used, particularly in therapeutic trials. Impaired QOL is shown across a spectrum of adrenal disorders, especially in Cushing's syndrome despite biochemical remission and chronic adrenal insufficiency despite glucocorticoid replacement. As QOL measures are highly subjective and specific to the patient, it must be measured in a standardized way, using robust measurement tools, and clearly reported in order to draw valid conclusions. In addition, potential confounders should be minimized. Overall, reporting quality was suboptimal and QOL was defined in only 5% of studies, the implication being that QOL was defined by its measurement.

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P024

Hyperandrogenism secondary to congenital portal hypertension

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Introduction
We report a rare case of hyperandrogenism associated with portal hypertension as a result of Alagille syndrome.
Case report
21-yr old female presented with primary amenorrhoea and mild hirsutism. There was no history of delayed puberty or acne. Past medical history: Alagille syndrome (biliary tree hypoplasia, liver disease, portal hypertension, splenomegaly, Barrett's oesophagus and pulmonary stenosis). Drug history: creon, ursodeoxycholic acid, alimemazine, vitamins. Her mother and sister have mild Alagille syndrome. Her mother also has PCOS. On examination: BMI of 24.2 kg/m^2 (160 cm, 62 kg), mild hirsutism, tanner 5 breast and pubic hair, and absent cliteromegaly.
Investigations
Total testosterone range 8 to 13 nmol/L (0.2–3.0), androstenedione 26 nmol/L (7–10.8), DHEAS 1.4 μmol/L (0.9 – 12), LH 18 iu/L (2–10), FSH 8.9 iu/L (2-10), 17-OH-progesterone 3.4 nmol/L (1–8.7), 17-β-Oestradiol 253 pmol/L, SHBG 116 nmol/L (30–75) , Free Androgen index 10% (<7.2), Bilirubin 33 μmol/L (0–21), ALP 342 iu/L (30–130). Low dose dexamethasone suppression test did not suppress testosterone (8 to 6.6). MR and ultrasound: normal adrenals, PCO appearances and 4 mm endometrium. Karyotyping was normal. Increased 24-hr urinary androstenetriol 1115 μg/24 h (mean 294) and α-cortolone 1339 μg/24 h (mean 675) noted, which are reported biochemical markers of portal hypertension.
Progress
Endometrium responded to progesterone challenge. Given liver transplantation is under consideration, 3 to 4 monthly oral progesterone challenge is planned.
Discussion
Relative increase in androgens is hypothesised as result of portovenal shunting of androgens from reduced liver catabolism of androgenic steroids, possibly aggravated by excess release from polycystic ovaries. Congenital portosystemic shunt causing hyperinsulinaemia may drive the ovaries to produce excess androgens.
Learning points
1. Hyperandrogenism can be caused by impaired hepatic steroid metabolism and increased urinary androstenetriol is believed to be the marker of this process.
2. Liver transplantation is definitive treatment, but triphasic oral contraceptives' utility is reported in literature.

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P025

Epidemiology of PPGLs – A population based approach

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Phaeochromocytoma/paragangliomas (PPGLs) are relatively rare tumours and the health burden of such tumours is not very well known.

Aim

This population based study aims to characterise all the phaeochromocytomas, paragangliomas and adrenal medullary hyperplasia diagnosed between 2007 and 2016 in Malta; looking into presentation, hormonal analysis, imaging characteristics and histology findings.

Results

16 patients were identified. 9 patients (56%) were males and age ranged from 21–62 years (mean 50 ± 14). The standardised incidence rate is 4.3/1,000,000/year. From the whole cohort 11 (69%) had phaeochromocytomas confirmed histologically, 3 (19%) had paraganglioma, and another 2 patients (12%) had adrenal medullary hyperplasia (adrenal medullary cell mass hyperplasia <1 cm, thought to be a precursor of phaeochromocytoma). 9 patients (56%) presented with hypertension, whereas 6 patients (38%) were found following investigation of an adrenal incidentaloma. All patients except 1 had either plasma free metanephrines or urinary fractionated metanephrines checked prior to surgery. In the phaeochromocytoma and adrenal medullary hyperplasia patients, CT was documented to be suggestive of phaeochromocytoma or an adrenal lesion not in keeping with an adenoma in 11 out of 13 patients (85%). Longest radiological tumour size ranged from 20–127 mm (mean 52 ± 28.9) All patients except 2 underwent surgical resection of the tumours. The latter 2 patients presented late with metastasis and died soon after diagnosis. Genetic testing was done in 6 patients (38%) and a VHL mutation was identified in one patient with phaeochromocytoma. 6 patients (38%) were found to have a malignant phaeochromocytoma on follow up.

Conclusion

This review highlights the extensive workup needed for patients with PPGL. Presentation can range from asymptomatic to life threatening clinical conditions. The high risk of malignancy found in our cohort emphasizes the need for long term follow up.

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P026

Ipilimumab induced hypophysitis

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Ipilimumab is an anti-CTLA-4 monoclonal antibody licensed for metastatic melanoma.

A 70-year-old female with metastatic malignant melanoma presented with anorexia, malaise and confusion two weeks after her fourth dose of Ipilimumab. She had a low serum sodium of 124 pmol/L on proton pump inhibitor and selective serotonin reuptake inhibitors, which were stopped and she was fluid restricted to 1.5 litres/day. Her urinary sodium was elevated 65 mmol/L. Serum cortisol was 19 nmol/L with no history of steroid use. A short synacthen test demonstrated a baseline cortisol of 18 nmol/L rising to 176 nmol/L at 90 minutes, and glucagon stimulation test baseline cortisol of 19 nmol/L to only 20 nmol/L at 120 minutes, GH rose to maximum <0.3 mIU/L. Her FSH and LH were low at 5.8 mIU/ml /0.4 mIU/ml respectively, oestradiol undetectable, TSH inappropriately low at 0.5 IU/ml for T4 of 6.1 pmol/L. ACTH was 3.2 pmol/L range (1.1–13.2). MRI pituitary was normal.

She was commenced on dexamethasone 0.75 mgs od and is currently well and continues on 0.75 mgs to date. 6 months later TSH has returned to normal 0.71 IU/ml (T4 19.2 pmol/L), Na 137 pmol/L.

Ipilimumab inhibits CTLA-4 receptors on T-cells, enhancing immune response and has been associated with immune related adverse events (irAEs). Hypophysitis accounts for 1–6% of Ipilimumab associated irAEs with some studies showing anterior pituitary antibodies in the serum of patients that developed ipilimumab induced hypophysitis (IIH). Measurement of these antibodies may help early diagnosis. Caturegli et al analysed autopsy pituitary samples of six patients treated with anti-CTLA-4. All samples expressed CTLA-4. The highest expression was found in the patient who had a pre-mortem diagnosis of IIH. Individuals with high pituitary expression of CTLA-4 may have a higher risk of anti-CTLA-1 hypophysitis.

There are currently no available tests to identify these individuals.

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P027

A comparison between short synacthen and long synacthen results in clinical decision making

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Introduction

Traditionally the long synacthen test (LST) is used in some centres to assess hypothalamic/ pituitary and adrenal (HPA) axis. Evidence that it offers advantage over short synacthen test (SST) is lacking. Whilst changing our local protocol we evaluated 27 patients who had both tests in our trust. We compared the impact of the results in clinical decision making.

Results

Mean age was 53 years. The indications for the tests were assessment for long term steroid induced hypoadrenalism (16), post pituitary surgery (6), post unilateral adrenalectomy (3), and other reasons (2). The cut off value for 30 min rise in cortisol was taken as 500 nmol/L in SST and peak cortisol response at 4–8 hours in LST was taken as 900 nmol/L. A recent assay change in cortisol measurement in our lab was applied to both the values (20% reduction). 12 patients (44%) had evidence for adrenal suppression on SST and 14 (51%) on LST. 2 patients had a good response on SST although but suppression on LST subsequently giving false negative/non-concordance rate of 7%. 3 patients had delayed response with peak at 24 hours which usually occurs in secondary adrenal failure. All 3 were being assessed for long term steroid induced hypoadrenalism and they also had evidence of adrenal suppression on SST. Overall there was good correlation between the SST and LST results.

Conclusion

There is considerable evidence for SST that it is an effective test to assess HPA axis. For clinical decision making SST is simple, cost effective, less laborious and reliable test.

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P028

Adrenal Incidentalomas- A Retrospective Analysis

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Adrenal incidentalomas is a common referral to endocrine department. We retrospectively looked at the number of referrals to the endocrine services with it over 1 year and their eventual outcomes. There were a total of 37 patients referred with adrenal incidentalomas to our department out of which 28 patients (76%) were non secretory, while 1 (3%) had catecholamine excess. 1 (3%) had mixed cortisol + catecholamine excess. 7(19%) patients either did not attend clinic or lost follow up. Most of the patients (29–77%) were in 5th-7th decade of life on their 1st visit to us. 30 (79%) incidentalomas size was <4 cms, 4 had size 3-3.9 cms and 3 >4 cms. There was no correlation between size and surgical outcomes. 2 patients who were secretory were >4 cms in size. 25 patients (68%) had CT reported as <10 HU, 6 (16%) had >10 HU requiring further imaging and 6 (16%) were not reported in HU. While investigating the secretory nature of the lesions we found that for most of the patients we carried out appropriate tests but we under investigated 3 patients as only 9 am cortisol was checked for 2 patients and no secretory tests carried out for 1. On the other hand we over investigated 11 patients as Aldosterone-Renin Ratio was checked for 10 normotensive patients and 1 patient had DHEA levels checked without appropriate reason. For the 37 patients referred to us, 25 eventually got discharged (68%), 4 got operated (11%), 4 lost follow-up (11%), 3 died due to other reasons (8%) and 1 is still on active follow-up (3%).

Conclusion

Majority of the patients referred for adrenal incidentalomas would be non-secretory, benign in appearance and most of them would be discharged without need for further follow-up. And we have to use the resources and guidelines wisely, taking care not to over investigate the patients whilst not under investigate at the same time.

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P029

The 2 year half-life of i.m. Trenbolone

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Case
A 33 year old gentleman presented with significantly raised testosterone levels, testicular pain, erectile dysfunction and weight loss. He denied use of anabolic steroids. Upon physical examination he looked muscular and tanned. Left testicle was tender with no palpable mass. Raised androgen levels (Siemens immunoassay) were confirmed by liquid chromatography tandem mass spectrometry (LC-MS/MS), ruling out assay interference. In view of his ongoing denial of substance misuse and genuine presentation, ultrasound testes and CT Chest-Abdomen were requested, to rule out the rare possibility of an androgen-producing tumour. Instead, we found a pulmonary embolism. During hospital admission his testosterone levels normalised, rising again after discharge. He continued to deny substance abuse but consented to urinary 'doping' investigations. His urine showed a raised testosterone-epitestosterone ratio of $>70{:}1$ (ref 0.1–6), and a testosterone concentration >800 ng/ml (ref <150), most likely due to exogenous testosterone use. In addition, urinary Stanozolol metabolites, Trenbolone, Boldenone, Nandrolone and their metabolites were detected. Whilst discussing these results he presented a vial of Trenbolone, expressing his surprise at its long half-life as he used this 2 years ago. We had arranged for psychiatric review immediately thereafter, during which he confessed ongoing substance abuse.
Conclusions/discussion
1. Use of anabolic steroids increases the risk for developing thrombo-embolic complications such as stroke, myocardial infarction and pulmonary embolism.
2. Routine clinical assays for serum LC-MS/MS androgen profiles and urine GC-MS steroid profiles are not set up for detection of steroids of abuse, however may be able to guide further analysis. Drug control centres are a potential resource in patients with anabolic steroid-related complications and ongoing denial.
3. Psychiatric advice on managing our patient has been valuable.

Table 1 Laboratory results.

	Presentation	During admission	After discharge
Testosterone (8–29) nmol/l	151.4	25.7	135.4
FSH (1–18), LH (3–35) IU/l	<1.0	<1.0	<1.0
Haematocrit (Ht) (0.42–0.54) l/l	0.52		
Alpha Fetoprotein (AFP) (0–10) kU/l	2		
Human Chorionic Gonadotrophin (HCG) (0–5) IU/l	<1		

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P030

Influence of vitamin D on outcomes following burn injury: An observational cohort study

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Introduction
Low levels of vitamin D are associated with higher mortality in critically ill patients. Studies on vitamin D levels in adult burn patients and their influence on clinical outcomes are scarce. Therefore, vitamin D status following thermal injury is often overlooked as its clinical implications are poorly understood.
Aim
To examine the relationship of major thermal injury on the vitamin D axis and the influence of vitamin D levels on outcomes in adult burn patients.
Methods
An observational cohort study in major burn injury patients (TBSA $\geq 20\%$) with patients followed up for 1 year following injury and blood samples taken at 10 timepoints. Vitamin D metabolites and their serum carrier vitamin D binding protein (DBP) were assessed using LC-MS/MS and ELISA respectively. Various clinical outcomes of patients were recorded, including wound healing, sepsis, multiorgan failure, mortality.
Results
38 burn patients with median TBSA of 42% were assessed. The inactive circulating form of vitamin D, 25-hydroxyvitamin D3 (25D3) and DBP were significantly reduced following major burn injury compared with healthy controls. Median 25D3 remained low.
Conclusion
Thermal injury affects vitamin D status, with low 25D3 levels predisposing patients to poorer prognosis. Data indicate that low serum 25D3 impairs tissue-specific antibacterial and wound healing responses in burn patients, potentially via tissue-specific activation and function. Supplementing with high doses of vitamin D to increase serum 25D3 may greatly improve health outcomes in burns patients.

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P031

Hypoadrenalism, Short Synacthen Test (SST) outcomes and glucocorticosteroid prescribing trend; A large private hospital experience in United Arab Emirates (UAE)

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Background
Diagnosis of adrenal hypofunction requires a high index of suspicion. A frequent cause is iatrogenic glucocorticosteroid prescribing hence the need for a clinical review after a prolonged course.
Aim
A review of glucocorticosteroid prescribing and auditing SST outcomes in a large private hospital.
Methods
Electronic records over an 18 month period were analysed for SST results, patient demographics and hospital-wide glucocorticosteroid prescriptions.
Results
Of 585000 recorded hospital visits, 59690 glucocorticosteroid prescriptions were issued with a mean duration of 2.5 weeks (range 1 to 900 days). 929 prescriptions had more than 2 month's duration. Most frequent formulation was nasal mometasone, 8412 (14%), mean duration 1.5 weeks (range 1 to 60 days). Oral formulations doses ranged 4 to 20 mg of prednisolone equivalent with mean duration 1.3 weeks (range 1 to 150 days).
68 patients (44 females) had SST for suspected hypoadrenalism. Average systolic BP was 112 (range 80–148) mmHg; average BMI was 26 (range 13.2 to 46.7) kg/m^2.
SST results were grouped according to cortisol assay times after baseline: group A had cortisol assayed at 30 and 60 minutes ($n=31(46\%)$; group B had 30 minute cortisol assay only ($n=37(54\%)$. In group A, 5(16%) failed at both 30 and 60 minutes. 11(35%) failed at 30, passing at 60 minutes, 8(26%) had a sub-optimal response at 30, passing at 60 minutes. 7(23%) passed both 30 and 60 minutes. In group B, 10(27%) failed with 4(11%) suboptimal response and 23(62%) passed.
Conclusions
To our knowledge, this is the first such study ever done in UAE. A much higher index of suspicion is required in proportion to longer duration of glucocorticosteroid prescriptions. SST needs standardising and gold standard ITT to be used in

unclear cases. Increasing such awareness among non-endocrine prescribers will ensure more patients are promptly diagnosed with adrenal insufficiency.

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P032

Large functional adrenocortical carcinoma presenting with hyperandrogenism and hypercortisolism

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Introduction

Adrenocortical carcinomas (ACCs) are rare; incidence is approximately 1–2 per million population per year. These arefrequently aggressive tumours that may or may not be functional. The primary potentially curative treatment for ACC is surgery with currently mixed opinion among experts regardingadjuvant Mitotane treatment.

The Case

60 years old female was seen in clinic for work up of incidental adrenal mass. CT abdomen showed a very large adrenal tumour measuring 21×16×14cmswithout evidence of metastases.

She had 5–6 month history of rapid onset facial hirsutism and frontal balding as well as clinical features of Cushings. She was alsonormokalaemic and hypertensive despite good concordance with three anti-hypertensives. Her 2×24 hour urine collections for Catecholamines and free Cortisol were normal. Her serum androgen levels weremarkedly elevated.DST failed to suppress Cortisol (564 nmol/L) with ACTH of 12 ng/L.

CT and PET scans didn't demonstrate distant metastases. She underwent right open adrenalectomy with steroid cover. Histopathology confirmed adrenocortical carcinoma with a higher proliferation rate of approximately 10–20% on MIB-1 immunostainingbut no capsular invasion.

Post-surgery her symptoms of hyperandrogenaemia, hypercortisolism and hypertension improved significantly. She was started on Adjuvant Mitotane treatment by oncologist. Repeat CT scan and PET scan didn't show recurrence.

Discussion

In this case, the adrenal tumour size was unusually large and interstingly without capsular invasion or metastases. The role of post-op Mitotane therapy is debatable. Our patient has responded well to surgery and Mitotane treatment. Evidence for adjuvant Mitotane interms of extending recurrence-free survival is based on a few retrospective studies. However, due to the frequentlyaggressive nature of adrenocortical tumours, it is generally recommended, as well as avoiding delays in the initiation of such treatment.

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P033

Can your hair tell your secret?

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Long-term exposure to cortisol carry health risk and its important to establish the cause and exclude exogenous steroid use before starting investigation for endogenous causes, we present a young man with clinical picture of Cushing but low random cortisol.

16 years old studying for his AS examinations at the time, presented to his GP with 5-week history of fatigue, weight gain of 2 stone in 18 months, insomnia, diarrhoea, left sided abdominal pain, reduced concentration, loss of appetite, dizziness and occasional headache.

On examination; BMI of 29.1, normal blood pressure, moon face and multiple striae over his trunk, axillae and abdomen. His visual fields were intact.

Initial investigation by GP; showed 9am cortisol of 100 followed by suboptimum short Synacthen test, he had been started on replacement dose Hydrocortisone (HC) and appointment booked with endocrine.

Seen in endocrine clinic, symptoms had not improved on HC, felt to have Cushingoid features clinically, Steroid had been gradually stopped and repeated testing 2 weeks later showed 9am cortisol of 192, Overnight Dexamethasone suppression cortisol less than 20, normal MRI Pituitary and Urinary steroid profile. He manages to lose five kg in weight.

We had a patient with Clinical appearance of Cushing's and suboptimal biochemistry our working diagnosis include cyclic Cushing's and exogenous steroid use based on clinical pictures and very low base line cortisol on his initial short Synacthen test. Patient had denied substance misuse on multiple occasions. patient had been asked not to cut his hair and a hair sample had been sent for steroid testing. preliminary result had showed high level of steroid for two consecutive months. We aware that hair test may not differentiate cyclic Cushing from exogenous use and our plan is to follow him clinically with repeated testing.

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P034

Management of ectopic ACTH syndrome: The birmingham experience

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Introduction

Ectopic ACTH syndrome (EAS) is a rare condition, accounting for approximately 10% of all Cushing's syndrome (CS). We assessed the experience managing this condition in our centre.

Methods

171 patients (105 female, 66 male) with elevated plasma ACTH concentrations were identified from local IT systems at a tertiary centre (University Hospitals Birmingham NHS Foundation Trust) between 2002 and 2015. An electronic case note review was completed to exclude other diagnoses and 15 patients with a suspected diagnosis of EAS were identified. Data on demographics, clinical features, investigations, treatment, underlying diagnosis and outcomes were obtained.

Results

The underlying diagnosis was occult/unidentified in 4 cases, whilst 3 bronchial NETS, 1 pancreatic NET with liver metastases, 3 medullary thyroid cancers (1 with MEN2a), 1 metastatic adenocarcinoma of parotid, 1 metastatic lung cancer, 1 oropharyngeal tumour and 1 lung lesion with negative histology were identified. CT was the initial imaging modality in 13/15 patients, and was positive in 54% of cases. PET identified a bronchial NET in one patient. Octreotide scans were positive in 2/6 patients with negative CTs. 11/15 patients were treated with metyrapone and 7 of these required hydrocortisone replacement. 7/15 patients underwent surgical resection of the primary tumour whilst 5 patients proceeded to bilateral adrenalectomy. On final clinical follow up 79% achieved eucortisolism, whilst the remainder were on a metyrapone/hydrocortisone block and replace regimen. Median follow up was 52 months (IQR 11–58). Mortality in the cohort was 33% (5/15), with death occurring in 3/4 patients with confirmed metastatic disease. All patients with occult disease were alive at final follow up.

Conclusion

EAS is caused by a diverse range of malignancies. PET and octreotide scanning may be of use in cases with negative cross-sectional imaging. Control of hypercortisolism was effective in our cohort. Occult disease was a positive prognostic finding.

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Bone and Calcium

P041

Studies of nuclear factor I/X (*NFIX*) mutations causing the Marshall-Smith syndrome (MSS)

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Marshall-Smith syndrome (MSS) is a congenital disorder characterised by developmental delay, failure to thrive and skeletal abnormalities such as accelerated osseous development, osteopenia, bullet-shaped middle phalanges and kyphoscoliosis. MSS is caused by truncating or frameshift mutations of the nuclear factor I/X (*NFIX*) gene, which encodes a ubiquitously expressed transcription factor that regulates expression of viral and cellular genes, including Bobby sox (*BBX*) and glial fibrillary acidic protein (*GFAP*). To further elucidate the role of *NFIX* mutations in MSS, we studied their effects on *BBX* and *GFAP* expression using fibroblast cell lines obtained from 5 MSS patients and 3 unaffected individuals. Informed consent was obtained using protocols approved by local ethics committees. The 5 MSS fibroblast cell lines were confirmed to have *NFIX* mutations in exons 6–8 by Sanger DNA sequencing and multiplex ligation-dependent probe amplification analyses, and these comprised 3 deletions (c.819-732_1079-948del, c.819-471_1079-687del, c.819-592_1079-808del), an insertion (c.1037_1038insT) and a duplication (c.1090dupG) that were all predicted to result in premature truncations. Transient transfection of N-terminal-FLAG tagged wild-type and MSS-mutant NFIX cDNA constructs in monkey kidney fibroblast (COS-7) cells followed by Western blot analysis confirmed that the MSS-associated *NFIX* mutants resulted in truncated proteins. Quantitative reverse transcription polymerase chain reaction (qRT-PCR) analysis using RNA from the human MSS fibroblasts showed no difference in *NFIX* transcript levels when compared to controls, indicating that the mutant transcripts were not cleared by nonsense-mediated-decay mechanisms. qRT-PCR and Western blot analyses using RNA and protein extracted from MSS fibroblasts and control fibroblasts showed no differences in *BBX* expression, but the *NFIX* c.1090dupG mutant was found to result in a 24-fold ($P<0.05$, $n=4$) decrease in GFAP protein. Thus, our results suggest that the majority of MSS-associated *NFIX* mutations are not acting via *BBX* or *GFAP*, but via other downstream target genes that remain to be identified.

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P042

LC-MS/MS measurement of parathyroid hormone PTH (1-34): Use in studying oral PTH (1-34) administration and possible diagnostic application in pseudohypoparathyroidism

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Background
Teriparatide PTH(1-34) is an osteoanabolic agent used in the treatment of osteoporosis. Measurement of PTH(1-34) can be useful in osteoporosis treatment and in the diagnosis of pseudohypoparathyroidism (PHP) by confirming administration of PTH(1-34)
Aims
1) To assess PTH(1-34) profiles obtained using standard Forsteo treatment compared to using a novel oral administration. 2) To confirm the PTH(1-34) in a PHP patient receiving PTH(1-34) as part of an Ellsworth Howard Test (EHT). 3) To perform a method comparison of oxidised/non oxidised forms of PTH(1-34) detected by LC-MS/MS with immunoassay.
Methods
Using a LC-MS/MS method, PTH(1-34) was measured in Pharmacokinetic (PK) profiles from a human double blinded study. Participants were given teriparatide either by a single SC injection (Forsteo,20 µg) ($n=6$); or in an oral dose of 0.69 mg ($n=4$), or 2.07mg ($n=6$) (EnteraBio). In an EHT, PTH(1-34), urinary PO4, and urine/plasma cyclic adenosine 3′5′-monophosphate (cAMP) were measured on samples before/after 20 µg Forsteo injection. Oxidised/non-oxidised forms of PTH(1-34) ($n=390$) measured by LC-MS/MS were compared against immunoassay (IDS; Boldon, UK).
Results
PK profiles showed rapid absorption of PTH(1-34) in plasma. The 2.07 mg oral dose achieved C_{max} of 271 pg/mL comparable to that of 20 µg Forsteo, but the injection form showed slower rate of plasma clearance ($T^{1}/_{2\,(injection)}=37.7$min, $T^{1}/_{2\,(oral)}=12.5$min). The EHT profile from a PHP patient showed a lack of cAMP response despite significant increase in plasma PTH(1-34) concentration. Method comparison showed LC-MS/MS results were correlated ($r^2=0.950$), but biased (-35.5%) against the immunoassay. The bias was caused partly by a matrix effect ($14.6\pm18.4\%$), cross reactivity of the immunoassay with PTH(1-84) ($7.1\pm0.45\%$) and to oxidised forms of PTH(1-34) ($23.9\pm6.1\%$).
Conclusion
Our LC-MS/MS method for PTH(1-34) can help validate the therapeutic use of osteoanabolic agents; confirm the lack of response to exogenous stimulation in EHT; and may explain the differences in responses to treatment due to oxidation of PTH(1-34).

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P043

Immunomodulation by vitamin D is associated with regulation of dendritic cell microRNAs

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The hormonally active form of vitamin D, 1,25-dihydroxyvitamin D (1,25D) acting via the vitamin D receptor (VDR) is a potent transcriptional regulator, with effects on skeletal and extra-skeletal physiology. We have shown previously that skeletal responses to 1,25D also involve regulation of microRNAs (miRNAs); small non-coding RNAs with an emerging role in epigenetics. To assess the role of miRNAs in innate immune responses to 1,25D we utilised *in vitro* models of human mononuclear cell-derived dendritic cell (DC) differentiation and maturation. DCs from $n=6$ healthy donors were differentiated for 5 days with IL-4 and GM-CSF, with or without 1,25D (10 nM). DCs were then matured for a further 24 hrs with combinations of LPS and/or 1,25D to generate 6 different DC phenotypes (iDC, itolDC, mDC, mtolDC, iDC+1,25D, mDC+1,25D). Candidate miRNA analyses showed that expression of miR155 and let-7i was elevated in mature mDC+1,25D relative to immature iDC+1,25D, underlining the potential for miRNA regulation in DCs. Quantitative RT-PCR array analysis ($n=6$ donor replicates) of 372 miRNAs closely associated with immune function showed that 44 miRNAs were regulated by LPS alone (>2-fold change), 174 were regulated by 1,25D alone, and 72 by both treatments. MiR-155 and miR-506 were suppressed by 1,25D ($P<0.05$) after 120 hour treatment in the presence of LPS. Preliminary pathway analysis data of predicted targets for miR-155 and miR-506 showed both miRNAs may target multiple transcripts. These data indicate that miRNAs are important targets for vitamin D in mediating innate immune responses by DCs. We postulate that miRNAs downregulated following 1,25D treatment may be involved in regulating inflammatory responses. Future work will focus on targeted over-expression or knockdown of specific miRNAs to explore the functional impact of these non-coding RNAs in mediating the immunomodulatory effects of vitamin D.

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P044

Disruption of the G-protein subunit α_{11} ($G\alpha_{11}$) interdomain interface causes autosomal dominant hypocalcemia type-2 (ADH2)

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Heterotrimeric G-proteins are important molecular switches that transduce extracellular ligand-binding at G-protein-coupled receptors (GPCRs) to intracellular signals. G-protein alpha-subunits (Gα) have two domains, a helical and GTPase domain, which provide structural stability and mediate GTPase activity, respectively. Gain-of-function Gα mutations cause endocrine conditions including McCune-Albright Syndrome, due to Gαs mutations, and autosomal dominant hypocalcemia type-2 (ADH2) due to Gα11 mutations. ADH2 arises as Gα11 mediates signalling by calcium-sensing receptor, a GPCR that regulates calcium homeostasis. Gα11 signalling activates phospholipase-C, inducing

intracellular calcium (Ca2+i) release and extracellular signal-regulated kinase (ERK) mitogen-activated protein kinase (MAPK) pathway activation. Studies of ADH2 mutations can provide important structure-function insights into G-protein roles in endocrinopathies. We therefore investigated two novel heterozygous ADH2-causing Gα11 missense mutations, Gly66Ser and Arg149His, that alter highly-conserved residues located between the helical and GTPase domains (the interdomain interface), and are predicted to disrupt interdomain contacts, thereby increasing G-protein flexibility and activating GDP-to-GTP exchange. We assessed the effect of Gα11 mutations on Ca2+i and MAPK pathways by expressing Gα11-wild-type, and Ser66 or His149 Gα11-mutants, in HEK293 cells stably-expressing CaSR. Ca2+i responses to extracellular calcium (Ca2+e) were assessed using a Fluo-4 fluorescent assay and NFAT-response element-containing luciferase reporter (measuring Ca2+i–induced gene expression); and MAPK responses assessed using a phospho-ERK (pERK) AlphaScreen assay and serum-response element (SRE)-containing luciferase reporter (measuring ERK-induced gene expression). The Ser66 and His149 mutants, when compared to Gα11-wild-type, led to: a leftward shift of the Ca2+i dose-response curves, with decreased mean half-maximal concentration (EC50) values, and elevated NFAT, pERK, and SRE responses. Treatment of Ser66- and His149-expressing cells with the CaSR negative allosteric modulator NPS-2143 normalised Ca2+i and MAPK responses. Thus, the Gα11 interdomain interface plays an important role in calcium homeostasis, and interdomain interface mutations can be normalised by CaSR allosteric modulators, indicating effective treatments for symptomatic hypocalcaemia.

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P045

Uniparental isodisomy as a cause of the autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) syndrome

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The autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) syndrome is an autosomal recessive disorder characterized by immune deficiency and the autoimmune destruction of endocrine organs such as the parathyroids, adrenal cortex and ovaries. APECED is caused by biallelic germline mutations of the autoimmune regulator (*AIRE*) gene on chromosome 21q22.3, which is expressed in thymic medullary epithelial cells and plays a key role in the development of immunological self-tolerance. We investigated 118 probands with suspected APECED for *AIRE* abnormalities by DNA sequence analysis, and identified biallelic mutations in 33 probands. Eighteen different *AIRE* mutations were detected, which comprised: eight frameshift; three splice-site; four missense; two nonsense; and one initiation codon mutation, which was predicted to alter gene transcription. The most frequent *AIRE* mutation was a 13 bp deletional frameshift (c.967_979del13; P.Leu323fs), which has been reported to commonly occur in the British population, and was identified in >25% of APECED probands, including in a 15 year old male, who developed hypoparathyroidism, hypoadrenalism and dental enamel hypoplasia. This proband, the son of non-consanguineous asymptomatic parents, displayed apparent homozygosity for the *AIRE* P.Leu323fs mutation, yet parental analysis of the *AIRE* gene revealed the paternal DNA to be heterozygous for the P.Leu323fs mutation, whilst this mutation was absent in the maternal DNA. To establish the mode of inheritance of the P.Leu323fs *AIRE* mutation, microsatellite analysis was undertaken using nine markers located across chromosome 21q21-21q22.3. This revealed that the proband was homozygous for all loci tested, and consistent with the proband having inherited two copies of the paternal mutant *AIRE* allele due to uniparental isodisomy. Thus, these studies demonstrate that bilallelic *AIRE* mutations may be caused by uniparental isodisomy rather than through an autosomal recessive mode of inheritance. Furthermore, uniparental isodisomy should be considered in APECED patients that harbour homozygous *AIRE* mutations, but are from non-consanguineous families.

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P046

Systematic *in silico* evaluation of rare genetic variants in G-protein alpha 11 (Gα11)

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The calcium-sensing receptor (CaSR) is a G-protein coupled receptor (GPCR) that maintains systemic calcium homeostasis by detecting alterations in extracellular calcium, which it transduces into signalling changes, mainly via the $G_{q/11}$ pathway, leading to a decrease in PTH secretion. The importance of CaSR is highlighted by studies of patients that harbour germline CaSR mutations, which lead to a gain of receptor function in autosomal dominant hypocalcemia (ADH), and a loss-of-function, in familial hypocalciuric hypercalcemia (FHH). Similarly, mutations in *GNA11*, which encodes the G-protein alpha-11 subunit ($G\alpha_{11}$), have been found to cause ADH type-2 (ADH2) and FHH type-2 (FHH2). We hypothesised that additional rare coding *GNA11* variants may influence $G\alpha_{11}$ functional activity and aimed to identify previously uncharacterised, non-synonymous, germline *GNA11* variants using online databases of large-scale sequencing projects, including the Exome Variant Server and 1000Genomes, comprising exomes from 69,713 unrelated individuals. We identified 61 missense *GNA11* variants, and selected those likely to be pathogenic for further study, based on a criteria of: a very low population frequency (0.000014); evolutionary conservation amongst orthologs and paralogs; and predicted severity on protein composition (using SIFT and polyphen-2). Using these criteria, we identified 9 variants for further analysis by three-dimensional homology modelling based on $G\alpha_q$, $G\alpha_s$ and $G\alpha_i$ structures. We found 3 variants (G51R, G66D, A231T) located at the interdomain interface, predicted to disrupt GDP binding; 3 variants (R147C, Q152H, D243G) located close to the $G\alpha_{11}$ switch 3 region, predicted to affect GDP-GTP exchange; 1 variant (R213W) located at the Gα-Gβγ and Gα-PLC interaction site; and 2 variants (N336S, R338C) located within the α5-helix that binds GPCR transmembrane domains and intracellular loops, predicted to disrupt GPCR-G-protein interaction. Thus, we have identified residues that may be important for $G\alpha_{11}$ structure-function activity, and further *in vitro* investigation is required to elucidate their effects on CaSR signalling.

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P047

A study on 24 hour urine calcium creatinine ratio in primary hyperparathyroidism (PHPT) and familial hypocalciuric hypercalcaemia (FHH)

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Background
Prevalence of FHH in hypercalcaemic patients with a raised PTH has been quoted as 1 in 20. Parathyroidectomy has no benefit and therefore it is important to exclude FHH prior to considering surgery.
Objectives
The aim of our study was to idenitify hypercalcaemic patients with a 24 hour urine calcium creatinine ratio (Ca/Cr) between 0.01–0.02 with a view to propose a cut-off ratio of 0.015 which will provide optimal discrimination between FHH and PHPT.
Study
We conducted a retrospective analysis of hypercalcaemic patients in a large tertiary centre, recording clinical and biochemical data, CaSR gene results, radiology and post-operative histology. The study group included 88 patients with hypercalcaemia with a mean age of 59 yrs (F:M ratio=3:1). Most patients had sporadic PHPT ($n=58$ (65%) confirmed by histology and post-op calcium. 24 hour urine Ca/Cr ratio was found to be <0.015 in 38 (43%) patients. In this group, 5 patients were CaSR gene mutation positive FHH and 17 patients (68%) had probable diagnosis of FHH with positive family history and/or no end organ damage. 2 patients who tested positive for CaSR gene mutation had a Ca/Cr of 0.014 even with normal vitamin D levels.
50 (56%) patients had a ratio >0.015, 90% of whom had a confirmed diagnosis of PHPT either by concordant imaging (USS and MIBI) or by parathyroid surgery. The remaining 10% of patients had a clinical diagnosis of PHPT as they were symptomatic and/or had end organ damage but were on conservative management. None of these patients were tested positive for CaSR gene or had clinical suspicion for FHH.

Conclusion
The major feature that distinguishes FHH from PHPT is a low 24 hour urine Ca/Cr ratio. In our study, we have shown that a Ca/Cr clearance ratio <0.015 has 100% sensitivity for FHH, 75% specificity and a negative predictive value of 100%. Based on this study, FHH should be strongly considered in all vitamin D replete patients with a 24 hour urine Ca/Cr ratio of <0.015.

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P048

Annual incidence of acute severe hypocalcaemia due to hypoparathyroidism: a 3 year consecutive study amongst patients with severe hypocalcaemia presenting to A&E

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Background
Patients with hypoparathyroidism may present acutely with hypocalcaemia and these patients may have multiple admissions; however, data on the incidence of acute and recurrent acute hypoparathyroidism are scarce in the literature.
Aim
We wished to determine: (1) the causes of severe hypocalcaemia amongst A&E attendances (2) the incidence of acute hypocalcaemia due to hypoparathyroidism amongst A&E attendances, and (3) the incidence of recurrent acute hypoparathyroidism.
Methods
All samples sent from a single A&E department for calcium measurement over a 3 year period (2014–2016) were screened. Severe hypocalcaemia was defined as a corrected calcium of <1.90 mmol/l. Samples were excluded if they were duplicates (from the same patient within 24 h) or if they were spurious (haemolysed or resolved on repeat). From the total patient cohort diagnoses were ascertained from the clinical record to ascribe a cause of hypocalcaemia. Recurrent hypocalcaemia was defined as two or more attendances with severe hypocalcaemia within 12 months.
Results
After excluding duplicates (7%) and spurious samples (35%), there were a total of 234 samples from 185 patients (mean age 56 year; 54% male) with one or more admission. Causes of severe hypocalcaemia included (% of patients): chronic kidney disease (28%), GI loss $\pm$ hypomagnesaemia (19%), alcohol $\pm$ hypomagnesaemia (13%), vitamin d deficiency (7%), hypoparathyroidism (11%) other/unknown (22%). 26 patients had recurrent episodes of acute hypocalcaemia: 4/26 surgical, 1/26 Di George and 1/22 CaSR mutation.
Conclusions
Given a local catchment area of approximately 700,000 the incidence of acute hypocalcaemia due to hypoparathyroidism was 13 per million per year. Recurrent acute hypoparathyroidism had an incidence of approximately 2–3 per million per year. Recurrent hypocalcaemia due to hypoparathyroidism is an uncommon presentation.

	% Severe hypocalcaemia ($n=185$)	% Recurrent severe hypocalcaemia ($n=26$)
Chronic kidney disease	28	37
GI loss +/− low Mg	19	11
Alcohol XS +/− low Mg	13	7
Hypoparathyroidism	11	19
Vit D defciency	7	4

Note: percentages do not add up to 100.

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P049

Predictors of nephrolithiasis, osteoporosis and mortality in primary hyperparathyroidism

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Introduction
Nephrolithiasis and osteoporosis are more common in people with primary hyperparathyroidism (PHPT), although the clinical factors associated with this risk are not well characterised. Recent evidence has suggested parathyroid hormone concentration, but not calcium, is associated with mortality in PHPT.
Methods
Retrospective analysis of all patients presenting to the Edinburgh Centre for Endocrinology & Diabetes with PHPT between 2006 and 2014 ($n = 611$).
Results
Renal stones were present prior to diagnosis in 10% and detected in 3.9% following diagnosis. Only 4.2% of all renal imaging detected asymptomatic stones following the diagnosis of PHPT. Logistic regression identified younger age ($P<0.001$) and male gender ($P=0.01$) as independent predictors of nephrolithiasis. Osteoporosis was present in 49%. Logistic regression identified higher age ($P<0.0001$), higher PTH ($P<0.05$) and lower creatinine ($P=0.001$) as independent predictors of osteoporosis. In patients where parathyroidectomy was not performed, higher PTH ($P=0.001$), older age ($P<0.0001$) and male gender ($P=0.03$) were independent predictors of mortality. Vitamin D concentration was available in 69%; when added to the mortality model, vitamin D deficiency ($P=0.03$), but not PTH, was independently predictive. PTH concentration was not associated with pre-existing cardiovascular disease, body mass index or age.
Conclusion
PTH concentration at diagnosis of PHPT was not associated with the risk of nephrolithiasis and was relatively weakly associated with the risk of osteoporosis. PTH was associated with subsequent mortality but this relationship may be driven by differences in vitamin D sufficiency. Determining, the dominant direction of this relationship is complex as PTH drives hydroxylation of cholecalciferol to active metabolites but vitamin D deficiency also stimulates PTH release. A large randomised trial of surgical intervention in cases not meeting current criteria for surgery is desirable.

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P050

Discontinuation of denosumab–real world experience from a single centre

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There is concern about rapid reduction in bone mineral density (BMD) and early rebound vertebral fractures following discontinuation of denosumab. Our aim was to review local experience of discontinuation of denosumab, changes in BMD and fractures in patients with osteoporosis.
Methods
A retrospective analysis was conducted for patients who discontinued denosumab between March 2011 & June 2016. Denosumab withdrawal(DW) was defined as a period >6 months from the last dose of denosumab. BMD before denosumab initiation and after DW were compared.
Results
Of 32 patients in DW group, mean age was 75.4 $\pm$10.7 years and 91% were women. 24/32 received $\geq$4 doses of Denosumab (median 6(IQR: 2.8)). 81.2%(26/32) received other bone-active treatments prior to denosumab. Bisphosphonates were administered in 15.6%(5/32) after DW.
12.5%(4/32) sustained 5 fractures (2 neck of femur and 3 vertebral) after DW at a mean interval of 20.2 $\pm$ 3.7 months. 3/4 of that group had received bisphosphonates prior to denosumab treatment and none received bisphosphonates during DW.
Mean time to DXA scan from the last dose of denosumab was 12.3 $\pm$ 10.6 months. An increase in *T*-score was observed at spine and hip (26.0% (IQR: 27.4) & 12.6% (IQR: 20.05)) up-to 20 months from DW. Beyond 26 months of DW there was a reduction in *T* scores at both hip and spine (-288.3% & -41.3% respectively).
Conclusions
We did not observe early onset, multiple vertebral fractures following DW. The first fracture in the DW group occurred at 15 months. Our data did not show a rapid early fall in BMD but beyond 26 months of DW there was evidence of a decline in BMD. We postulate that pre-treatment with bisphosphonates may protect against rapid bone loss and rebound fractures following DW. Our current practice is to administer at-least a single dose of IV zoledronic acid prior to DW.

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P051

1,25-dihydroxyvitamin D deficiency in haemodialysis patients is corrected by vitamin D supplementation

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Reduced renal synthesis of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) from 25-hydroxyvitamin D (25OHD) in end stage renal disease (ESRD) results in low serum $1,25(OH)_2D$. This appears to be due to reduced renal cell function and elevated serum fibroblast growth factor 23 (FGF23). Treatment strategies have therefore focussed on $1,25(OH)_2D$ or its synthetic analogues, alfacalcidol or paricalcitol. However this overlooks 25-hydroxyvitamin D (25OHD) deficiency, which is common in ESRD. In the current study a subset of 33 haemodialysis patients from Coventry and Warwickshire were assessed during routine supplementation with vitamin D_3 to raise serum 25OHD (colecalciferol supplementation: serum 25OHD <50 nmol/L repletion dose of 40,000IU for 3 months, ≥ 50 nmol/L maintenance dose of 20,000IU fortnightly, >150 nmol/L stop and recheck in 3 months). Multiple serum vitamin D metabolites were measured using liquid chromatography-tandem mass spectrometry at baseline (T0) and after 12 months supplementation (T12). Serum 25OHD increased significantly from 37.4 ± 4.38 nmol/L at T0 to 117.7 ± 6.61 nmol/L at T12 ($P < 0.001$) with 88% of patients ≥ 75 nmol/L. Serum $1,25(OH)_2D$ also increased significantly in 94% of patients ($P < 0.001$) from 43.4 ± 4.75 pmol/L to 91.2 ± 5.30pmol/L at T12. Parallel analyses showed that serum calcium increased following colecalciferol supplementation (T0 *vs.* T12, 2.35 ± 0.03 to 2.45 ± 0.03 mmol/L, $P < 0.05$), no hypercalcaemia was associated with colecalciferol supplementation. At T0 levels of $1,25(OH)_2D$ and $24,25(OH)_2D$ correlated with 25OHD ($P < 0.05$). However, once 25OHD was replete (T12) this correlation was lost. Serum calcium correlated with $1,25(OH)_2D$ at T12, but not at T0. These data suggest serum 25OHD was limiting at T0. This study indicates that vitamin D repletion in haemodialysis patients is safe and significantly increases serum $1,25(OH)_2D$. Demonstrating that kidneys with a low GFR and elevated FGF23 retain the ability to synthesise $1,25(OH)_2D$ in a substrate-dependent fashion. Complementing $1,25(OH)_2D$ analogue treatment with colecalciferol may prove effective in managing bone and mineral disorders associated with renal disease.

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P052

Retrospective audit of the use of cinacalcet for the treatment of primary hyperparathyroidism in adults against the NHS England prescribing criteria

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Method
We carried out a retrospective audit of baseline data for patients under our care with primary hyperparathyroidism on cinacalcet therapy, against the NHS England Clinical Commissioning Policy (July 2016). Patients with secondary hypercalcaemia due to end stage renal failure were excluded.
Results
40 patients were identified, 9 men and 31 women, with an age range of 32–89 years (median age 78). 3 patients were under 50 years of age. Pre-treatment, 21 patients (52,5%) had severe hypercalcaemia (serum calcium >3 mmol/L), 11 (27.5%) had moderate hypercalcaemia (serum calcium 2.85-3 mmol/L) and 8 (20%) had mild hypercalcaemia (serum calcium <2.85 mmol/L). The median baseline vitamin D was 40 nmol/L (range 8 – 151 nmol/L); 26 patients (65%) had a vitamin D >50 nmol/L. 19 patients (47.5%) had symptomatic hypercalcaemia. 11 patients (27.5%) had a history of renal stones. All patients met at least one of the indications for parathyroidectomy. 15/40 (37.5%) were unfit for surgery; 12/40 (30%) refused surgery; and 13/40 (32.5%) were treated with cinacalcet whilst awaiting surgery.
Conclusions
Our results show that to meet the NHS England prescribing criteria for cinacalcet we need to change some aspects of our previous practice, including the use of cinacalcet for patients with a serum calcium <2.85 mmol/L and the use of cinacalcet prior to parathyroidectomy operations. We also need to ensure all patients are vitamin D replete. We are now including all medically managed patients in our parathyroid MDT discussions and auditing cinacalcet prescribing prospectively.

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P053

Critical evaluation of biochemical and imaging diagnostic assessment in primary hyperparathyroidism

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Introduction
The performance of biochemical and imaging investigations in contributing towards successful surgical outcomes is not well characterised in PHPT.
Methods
Retrospective analysis of all patients presenting to the Edinburgh Centre for Endocrinology & Diabetes with PHPT between 2006 and 2014 ($n = 611$). Parathyroid surgery was performed in 44.8%.
Results
PTH was greater than 2x ULN in 34.3%, above ULN but not greater than two-fold in 54.5% and within reference range in 11.1%. Vitamin D deficiency was present in 32.6% (135/413). Urine CCCR was <0.01 in 18.1% of surgically confirmed cases of PHPT. Vitamin D status and spot-sample versus 24-hour urine collection was not associated with differences in CCCR. 247/375 (65.9%) neck ultrasound scans identified an adenoma. In surgically confirmed cases, only older age ($P < 0.001$) was identified as a risk factor for failing to identify an adenoma on ultrasound. Ultrasound determined laterality was correct in 172/182 (94.5%) cases at surgery where an adenoma was identified. 144/220 (65.4%) sestamibi scans showed significant uptake – the following factors were associated with uptake: greater tumour dimension ($P < 0.001$), higher PTH ($P < 0.01$) and higher adjusted calcium ($P < 0.05$). Structural lesions were noted in 64/93 (68.8%) SPECT CT scans. Surgical failure was 5% where one imaging modality was employed, 13.7% with 2, 10.5% with 3 and 20% with 4. Thyroid US was associated with 7.8% treatment failure, Sestamimbi with 11.6%, SPECT CT with 8.6% and 4DCT with 30.8%.
Conclusion
The vast majority of PHPT is associated with a frankly elevated PTH concentration. The likeliest diagnosis in patients with low CCCR is still overwhelmingly PHPT. Confident diagnosis of an adenoma on US is associated with satisfactory surgical outcome. When multiple imaging modalities are required, success rates are predictably lower. A gold-standard modality is required, early experience with 11C-Choline PET holds some promise.

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P054

Review of denosumab therapy In a Scottish population

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Introduction
Denosumab is a human monoclonal antibody against the receptor activator of nuclear factor-kB ligand, to reduce bone resorption by limiting maturation of osteoclasts. It has been approved for use in Scotland in patients with a bone mineral density (BMD) *T*-score of between -4 to 2.5 who are unable to take bisphosphonates. We aimed to analyze the effects of denosumab on BMD and fracture rate in a cohort of patients who have completed a 3-year cycle of therapy. We also aimed to review the underlying indication to therapy and discontinuation rates.
Methods
Ninety-one patients were identified through the mineral metabolism service who were receiving denosumab within the Queen Elizabeth University Hospital in Glasgow. Baseline demographics and BMD pre- and post-treatment was obtained through clinical notes.
Results
The mean age of patients receiving denosumab therapy was 71.5 years. The indications for treatment were poor result with previous therapy ($n=41$), bisphosphonate intolerance (20), renal impairment (17), fractures during bisphosphonate holiday (7), learning difficulties (3) and others (3). Thirty-five patients did not have a post-treatment dual-energy X-ray absorptiometry (DXA) scan, of these 28 stopped denosumab therapy prematurely due death, non-compliance or declined further treatment. Of those where we had post-treatment data, we divided the change in BMD into those whose BMD had deteriorated, increased by 0–5%, 5–10% and more than 10% improvements. Fifteen patients sustained a new fracture during denosumab therapy. 13 additional patients sustained a new fracture but had not completed a full course of treatment.

	Percentage change			
	<0% (i.e. worsening)	0–5%	5–10%	>10%
Vertebra BMD	4	15	15	22
Hip BMD	18	16	17	4

Conclusion
The majority of patients had a >10% improvement in vertebral BMD while hip BMDs did not change as markedly. The drawbacks to the study include the small number of patients and the inherent frailty of our population which is reflected in the high mortality. We also have a proportion of patients who did have follow-up DXA testing and may influence the overall results.

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P055

The incidence of Bisphosphonate related Osteonecrosis of the Jaw (BONJ) in patients treated with oral bisphosphonates for osteoporosis

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Introduction
BONJ is a recognised complication of bisphosphonate treatment (both oral and intravenous). Data are sparse with the reported incidence of BONJ in the oral treatment of osteoporosis between 0.01% to 0.067% or alternatively described as 1.04 to 69 per 100,000 patient-years. This study aimed to estimate the incidence of BONJ in patients taking oral bisphosphonates as a treatment for osteoporosis.
Methods
Forth Valley Health Board (GP Practice population 317,641, Forth Valley Health Board data, 1/10/16) has one treatment centre for BONJ at Forth Valley Royal Hospital. From September 2015 to September 2016 all cases of BONJ were recorded. Data on prescriptions for bisphosphonates dispensed in the community were extracted from NHS Scotland's Prescribing Information System for the period September 2015 to September 2016 inclusive.
Results
In 2015–16, 4978 individuals in Forth Valley had oral bisphosphonate prescriptions dispensed in the community. In 2015–16 there were 8 cases of BONJ. 3 cases were receiving intravenous bisphosphonates (cancer therapy) and were excluded. 5 individuals, with post code addresses in Forth Valley, were taking oral bisphosphonates for osteoporosis treatment (4 female, 1 male, age range 51–90 years with a median of 84 years, average 73 years). They were receiving oral alendronic acid (70 mg weekly) with a range of elapsed treatment time to BONJ of 29 to 117 months (median 47, average 60.2). Tooth extraction appeared to be the precipitating factor in 4 of the 5 cases. In our study there were no recorded cases of osteonecrosis of the jaw without the use of bisphosphonates. The incidence of BONJ for those treated with oral bisphosphonates for osteoporosis was 0.1%.
Conclusion
Studies have shown a significant variation in the incidence of BONJ. This study suggests an incidence, in our population, higher than previously reported. The reason for this is not clear.

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P056

Audit on parathyroid scans in patients with surgically managed primary hyperparathyroidism

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Background
Management of PHPT includes successful localization of parathyroid adenoma(s) by nuclear imaging and ultrasound scans allowing focused or minimally invasive surgery. Our aim was to assess the accuracy of parathyroid imaging in surgically-treated patients with primary hyperparathyroidism (PHPT) by correlating the imaging findings with surgical findings and cure of hyperparathyroidism. We also compared the surgical outcomes in patients with concordant and discordant imaging.
Patients and methods
We performed a retrospective review of 92 patients who were operated for PHPT between 2012 and 2016. Mean age 62±24 years, calcium 3.37±0.9 mmol/l, PTH 27.47±24.39 pmol/l. 82 patients had both ultrasound and 99mTc-MIBI/123I subtraction SPECT/CT scans. Findings on both scan - individually and together - were compared with surgical findings and outcomes using pre-defined criteria.
Results
50(62%) patients had concordant scans and 32(38%) had discordant results. Of the latter, in 27(31%) patients one or both scans failed to localise an adenoma and in 5(6%) patients adenoma was localised on opposite sides. Cure rate was 84% and 94% (P=ns) in patients with discordant and concordant imaging respectively. Patients with discordant scans had lower calcium, lower PTH and smaller adenoma, which weighed less as compared to those with concordant scans ($P<0.05$ for weight, P=ns for rest). The sensitivity and positive predicted value (PPV) of radionuclide (81% and 90%) and ultrasound scans (76% and 88%) were comparable, while concordance imaging had a sensitivity of 66% with PPV of 96%.
Conclusion
Sensitivity and PPV of US and RN scans was comparable and in line with published values in the literature. Discordance rate was high and in a majority of patients it was due to non-localisation. Cure rate for patients with discordant scans was lower than in patients with concordant scans, but the difference was not statistically significant, possible due to small numbers.

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P057

Imaging in primary hyperparathyroidism; does it affect our referral pathways for surgery? Results of an audit

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Introduction
The 4th International Workshop on asymptomatic primary hyperparathyroidism (PHPT) has set criteria for surgical intervention and suggests that a percentage of patients can be managed conservatively. Imaging is indicated only pre-operatively to determine the optimal surgical approach.
Patients and methods
We completed an audit on the use of Sestamibi, clinical and biochemical data in patients with PHPT.
Results
117 consecutive patients undergoing a Sestamibi scan over 2.5 years were identified. 11 (9.4%) requests were considered inappropriate (e.g. secondary hyperparathyroidism, hypercalcemia of malignancy). Of the 106 patients with PHPT, 71 (67%) had at least one indication for surgery or patient's preference for surgery clearly documented in notes.
Mean age was 62.6±14.3 and 76% were females. Mean adjusted calcium levels were 2.75±0.14 mmol/l, PTH 12.2±5.6 pmol/l and 25OHD 65.3±28.9 nmol/l. 18.9% of patients had a history of kidney stones and 23.6% had osteoporosis. DXA data were available for 82 patients. Mean T-score was −1.1±1.6 for lumbar spine, −1.2±1 for femoral neck and −0.7±1 for total hip.
Of the 106 patients, 62 (58%) had surgery, 57 of whom in our hospital and data on outcomes were available.
Of 35 patients who had no indication for surgery, 20 had negative Sestamibi and 3 (15%) of them had parathyroidectomy, while 15 had positive Sestamibi and 13 (86.7%) of them had parathyroidectomy. Surgery was successful in 15 (93.6%).
Among 71 patients with an indication for surgery, Sestamibi was positive in 30 (42%) patients and 41 patients in total (58%) had parathyroidectomy. Surgery was successful in 40 (95%).

Conclusion
Patients with positive imaging were more likely to be referred for surgery, even in the absence of a clear indication.
We suggest that Sestamibi scans are requested only by endocrinologists or surgeons and only when surgery is planned.
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P058

Audit of adjusted calcium and serum 25-OH vitamin D screening and replacement therapy prior to Zoledronic acid infusion at University Hospitals Birmingham

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Background
Zoledronic acid infusions are licensed for the treatment of osteoporosis and other bone disorders. Hypocalcaemia, a common side effect, increases the risk of complications. The risk of hypocalcaemia is further increased by a deficiency in 25-OH Vitamin D (VD). Pre-dose screening (PDS) is necessary to detect sub-optimal levels of serum VD and adjusted calcium (AC) early to avoid delayed treatment.
Objectives
Audit adherence to University Hospitals Birmingham (UHB) trust guidelines regarding:
1. The completion of PDS of serum VD and AC prior to administration of Zoledronic acid.
2. The appropriate management of adequate and sub-optimal serum VD results.
Methods
The study sample ($n=51$) was recruited from 284 patients. Included patients initiated Zoledronic acid in 2015, received two doses by December 2016, and failed to fulfil any exclusion criteria. The PDS results and management of these patients were recorded for both doses, highlighting 102 doses for analysis. Patient supplementation history was also recorded.
Findings
There was 100% adherence to the PDS standard. It was found that a greater proportion of patients had sub-optimal VD than AC levels (18.6% vs 0% respectively).
There was 98% adherence to the overarching management algorithm. Management of those with adequate VD levels showed greater adherence to guidelines compared to those with sub-optimal levels (100% vs 89.5% respectively).
Conclusions
The high adherence to PDS and management guidelines is a positive finding with only 2% of management decisions being off-protocol due to specialist decision. Interestingly, seven patients with adequate VD levels on initial screening were found to have sub-optimal levels on PDS for the subsequent dose. This offers support for trust guidance to repeat PDS, however, there is scope to investigate this by cost-benefit analysis.
Additionally, 63% of patients with sub-optimal VD were supplemented, highlighting potential for further research into the efficacy of supplementation and patient compliance.
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P059

Spontaneous inpatient parathyroid autoinfarction and remission of primary hyperparathyroidism from a mediastinal adenoma

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Ectopic parathyroid adenomas have a low imaging incidence quoted at 1.4% in patients undergoing investigation for primary hyperparathyroidism with a prevalence of 6–30%. These are reported to have a more clinically severe manifestation of the disease, frequently with higher calcium levels and bone disease. Remission due to parathyroid infarction is a rare occurrence. We report a 54-yr Afro-Carribean/mixed race female who presented with lethargy, weight loss and reduced oral intake for 3 months. She reported no significant past medical history and was not on any medications. Admission biochemistry revealed significantly raised calcium of 4.58 mmol/l, PTH 51.6 pmol/l, Alk Phos 190 IU/l indicating primary hyperparathyroidism with severe Vit D depletion <12.5 nmol/l. She was admitted to the acute medical unit, treated with IV normal saline, received 90 mg of IV pamidronate and high dose Vit D supplementation. US neck and CT scan confirmed right lower pole parathyroid adenoma, extending into the mediastinum with associated bone disease with patchy bone marrow changes throughout her spines suggestive of Brown Tumours on MRI scan. Interestingly 10 days later she developed symptomatic hypocalcaemia with spontaneous reduction of PTH requiring treatment with IV calcium, this is likely related to the fact that she might have developed hungry bone syndrome following spontaneous resolution of her hyperparathyroid state or parathyroid intoxication. MRI neck scan showed 44 mm cystic lesion lying on the deep aspect of the right lobe of the thyroid with enhancing tissue suggestive of possible viable adenoma or perilesional inflammation. The overall picture was consistent with parathyroid infarction. 6 weeks post admission, her PTH level normalisedand calcium remained within range. Spontaneous infarction of the parathyroid has been reported but is rare. Published reports have recommended careful monitoring and consideration of parathyroidectomy as regeneration may occur.

	Calcium (mmol/l)	**PTH** (pmol/l)	**Alk** Phos (IU/l)
On admission	4.58	51.6	190
10 days post treatment	1.88	17.6	534
On discharge (2 wks post)	2.29		429
6 wks post presentation	2.40	6.8	189

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P060

Review of parathyroid imaging and subsequent surgical findings in primary hyperparathyroidism – do they correlate?

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Introduction
Primary hyperparathyroidism is the most common cause of hypercalcemia in the ambulatory setting. Once the diagnosis has been confirmed, imaging of the parathyroid glands is performed locally with a combination of ultrasound scan (USS) and sestamibi/single-photon emission computed tomography (SPECT CT) to localise a parathyroid adenoma prior to surgery.
Method
Data was collected on patients undergoing parathyroid surgery between November 2012 and December 2014. We analysed the following:
1. Pre and post-operative calcium and parathyroid hormone (PTH) levels
2. USS report
3. Setstamibi/SPECT CT report
4. Location and histology of parathyroid gland(s) removed
5. Post-operative calcium and PTH levels.
Results
21 patients underwent parathyroidectomy. In 19 patients the location of the removed parathyroid gland was documented. All patients had undergone both USS and sestamibi/SPECT CT imaging.
Mean age was 63.3 years and 80% were female. Mean pre-operative calcium was 2.75 mmol/l and mean PTH 16.9 pmol/L. Surgical findings included eight left sided parathyroid adenomas (42.1%), ten right sided (52.6%) and one in the mediastinum (5.3%). One patient (4.7%) had two parathyroid glands removed which were both on the right side. Histology indicated 19 parathyroid adenomas (90.4%), one parathyroid neoplasia (4.7%) and one (4.7%) thyroid tissue. 52.6% had ultrasound and operation findings that correlated. 66.8% had sestamibi and operation findings that correlated. Eight patients (42.1%) had both ultrasound and sestamibi results that matched surgical findings. 20/21 patients had a biochemical cure (normal calcium postoperatively; mean 2.40 mmol/l.) 16/17 patients also had a PTH measured within normal limits; mean value of 5.14 pmol/L.

Conclusions
Sestamibi/SPECT CT scan imaging was slightly more sensitive than USS. Imaging was useful for localising parathyroid glands pre-operatively in around two thirds of patients. 95.2% of patients had their primary hyperparathyroidism cured surgically. No surgical complications were reported.

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P061

Prevalence of Kidney Stones and Osteoporosis in Patients with Primary Hyperparathyroidism (PHPT)

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Aim
To evaluate the prevalence of kidney stones and osteoporosis in a cohort of patients with a confirmed diagnosis of primary hyperparathyroidism (PHPT).
Study Design
This retrospective study reviewed the clinical records of patients with a confirmed diagnosis of PHPT in a single tertiary referral centre for metabolic bone disease over a period of 6 years (January 2010 – December 2015).
Patients
There were a total of 258 patients included in the study. 206 women (173 post-menopausal and 33 pre-menopausal) and 52 men with mean age of 63.5 + 14.84 years.
Method
The clinical records of 258 patients were scrutinised to determine the prevalence of kidney stones (as identified by abdominal ultrasound or X-ray or computed tomography scan) and osteoporosis (defined as bone mineral density T-score of < -2.5 measured by dual-energy X-ray absorptiometry [DXA]). The prevalence of kidney stones and osteoporosis were compared between the symptomatic and asymptomatic PHPT patients.
Results
The prevalence of kidney stones in those who had undergone renal imaging was 13.86% (28 out of 202). There was no difference in the prevalence of kidney stones between the symptomatic and asymptomatic patients (15.45% versus 11.96%, $P=0.5428$). The prevalence of osteoporosis was found to be 43.62% (from 188 patients who had bone DXA scan). There was also no difference in the prevalence of osteoporosis between the symptomatic and asymptomatic patients (43.43% versus 43.82%, $P=1.0000$).
Conclusion
Kidney stones and osteoporosis are common in both symptomatic and asymptomatic PHPT patients. The results from this study provide further evidence of the need for a more rigorous and consistent evaluation of the kidneys and skeleton of patients diagnosed with PHPT in order to identify and manage these well- known end-organ complications appropriately.

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P062

Delphi panel to define patients with chronic hypoparathyroidism 'not adequately controlled on standard therapy'

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Chronic hypoparathyroidism (HypoPT) is a rare endocrine condition characterised by hypocalcaemia and deficient or absent parathyroid hormone. The recent European Society of Endocrinology Guidelines outline recommendations for treatment and monitoring of chronic HypoPT in adults. A Delphi panel was conducted to agree upon the characteristics that define 'not adequately controlled on standard therapy' where this relates to patients with chronic HypoPT.
A Delphi panel was carried out initially via face-to-face interviews and subsequently via electronic questionnaires. Three rounds of questions and controlled panellist feedback were given to a panel ($N=10$) of HypoPT UK clinical experts. At each round, panellists were asked to consider 'not adequately controlled on standard therapy' according to three different patient presentations; (1) 'abnormal' biochemical levels but presenting 'well', (2) 'normal' biochemical levels, presenting as 'unwell', (3) 'abnormal' biochemical levels, presenting as 'unwell'. Panellists rated the importance of fifty-five variables ('characteristics'), previously identified from the literature, and grouped according to patient characteristics, biochemical levels, HypoPT comorbidities and patient reported symptoms. Consensus was considered as reached when $\geq 80\%$ of panellists agreed upon the importance level of a variable.
Across the three patient presentations, several variables reached consensus. Patient presentation 1 found the most important variables were biochemical levels and HypoPT comorbidities. Patient presentation 2 found the most important variables were those describing patient reported symptoms (e.g. 'tingling or numbness'). For patient presentation 3, the variables that described biochemical levels, HypoPT comorbidities, and patient reported symptoms were all deemed important for characterising these patients.
This study is a first step to understanding the characteristics considered important by UK clinical experts for defining patients with chronic HypoPT, that are 'not adequately controlled on standard therapy' according to their different presentations. The list of characteristics derived should now be tested by UK clinicians for their applicability in clinical practice.

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P063

A difficult case of metastatic parathyroid cancer with refractory hypercalcaemia and medication-related osteonecrosis of the jaw

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We present the case and management of a 76 year old man who developed medication-related osteonecrosis of the jaw (MRONJ) as a result of 12 years of bisphosphonate and denosumab treatment for hypercalcaemia in the setting of metastatic parathyroid carcinoma.
Within two years of his original parathyroidectomy, he had metastatic recurrence diagnosed with progressive hypercalcaemia; imaging revealed three pulmonary nodules consistent with metastases.
His hypercalcaemia was refractory to treatment with a number of bisphosphonates and high dose cinacalcet (90 mg tds). We have previously described how his calcium levels eventually stabilised on denosumab 120 mg monthly from peak corrected calcium 3.35 mmol/L to 2.74 mmol/L (R.I. 2.2–2.6) alongside cinacalcet therapy.
Despite medical management his PTH levels rose consistent with progression of his metastatic disease. Two microwave ablative procedures of his pulmonary metastases were undertaken with good, albeit temporary result. Peak PTH pre-ablation was 148.3 pmol/L which reduced to 15pmol/L initially with normalisation of calcium.
Subsequently he developed severe painful symptoms of the mandible with swelling, submandibular fistulas, pus discharge and intra-oral bone exposure, in keeping with a diagnosis of MRONJ. A CT scan confirmed the presence of extensive osteonecrosis to the mandible, which was not surgically resectable.
Patients with parathyroid carcinoma historically have died of the complications of hypercalcaemia. Importantly our patient had significant morbidity when hypercalcaemic due to symptoms of fatigue, poor mobility and intermittent confusion which affected his quality of life.
Given a lack of robust data to suggest that stopping anti-resorptive therapy leads to any significant improvement of MRONJ, it was decided via multi-disciplinary discussion to continue denosumab +/− bisphosphonate therapy to prevent life-threatening complications and maintain stable calcium levels.
His MRONJ is being managed conservatively with antibiotics and analgesia.

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P064

Milk-alkali syndrome in the post PPI era

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The milk – alkali syndrome was well known in the pre-proton pump inhibitor era when remedies for peptic ulcer included a large amount of calcium and sodium bicarbonate resulting in hypercalcaemia, metabolic alkalosis and often acute kidney injury. In a study done from 1998 to 2003, milk alkali syndrome was the cause of hypercalcaemia in 8.8 percent of the cases which is a significant percentage, so awareness about it is important.
We present a 76 year old gentleman who developed milk alkali syndrome inadvertently. He was admitted under urology for surgery on his bladder tumour but had a prolonged stay due to surgical complications. His background illness included hypertension, psychosis and depression. He was on no offending medications.
He was started on milk 200 ml TDS following advice from dietitians. He developed hyperkalaemia and acute kidney injury which was treated with intravenous fluids and Calcium gluconate. His Calcium, which was normal pre-admission, increased with and this thought to be secondary to the IV calcium. His hyperkalaemia was persistent and he was started on oral sodium bicarbonate. Calcium level increased to 3.41 after this.
Other results showed a suppressed PTH, normal phosphate, low Vitamin D level and pH of 7.33. We stopped both the milk and the oral bicarbonate and continued IV fluids for 48 hours, which resulted in normalisation of calcium level. He was also treated with cholecalciferol, although the suppressed PTH suggested the hypercalcaemia was unrelated to the Vitamin D deficiency.
This case highlights the importance of a good medications review and considering rarer causes of hypercalcaemia. With the increase in use or oral caclium in the management of osteoporosis and its easy availabitlity over- the -counter use, we should consider milk alkali syndrome as a cause of hypercalcaemia, especially with a suppressed Parathyroid hormone level.

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P065

Primary hyperparathyroidism – A retrospective review

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Primary Hyperparathyroidism is one of the common endocrine disorders seen in an endocrine clinic. We retrospectively analysed patients referred with primary hyperparathyroidism over 1 yr (Oct 2013 - Sept 2014) and followed them over next 30 months. Patients with isolated secondary hyperparathyroidism were excluded. Few had secondary hyperparathyroidism in addition to primary hyperparathyroidism.
50 patients with primary hyperparathyroidism were referred to the endocrine services over 1 yr, out of which 62% (31 patients) were managed conservatively. Of the 50 patients 40% (20 patients) were in 7th decade of their lives, 10% (5 patients) in 8th decade while 16% (8 patients), 14% (7 patients), and 20% (10 patients) were in 4th, 5th and 6th decades respectively. Detailed analysis of the cohort showed that with increasing age there was less likelihood for them to be operated. In 19 patients who had parathyroidectomy, 74% (14 patients) were operated under 70 yrs of age. Only 5% (1 patient) had post-op hypocalcemia while 10% (2 patients) had persistent hypercalcemia. Of the rest of the 31 patients who were not operated only 4% (2 patients) had fractures over the next 30 months- 1 had normocalcemic hyperparathyroidism while the other was not willing for surgery. In the medically managed group, over the 30 months, BMD was not checked in 32% (10 patients- 2 patients (6%) failed to attend followup, 2(6%) moved out of area, 1(3%) died, 3(9%) had mild disease & 2 patients (6%) were still under surveillance), no renal imaging was done in 29% (9 patients) & no 24hr urine calciums were done in 80% (25 patients).
Conclusions
Rates of primary hyperparathyroidism rises with increasing age and not all are required to be operated upon. In accordance with the guidelines for asymptomatic hyperparathyroidism, we saw very less complication rate in terms of fractures but we fell short by not doing 24hr urine calciums & imaging of kidneys for stones in all patients that were not operated.

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P066

Bilateral atypical femoral fractures after only 4-years of bisphosphonate therapy

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We report a 64-year old female with a background of T2DM, renal transplantation requiring ongoing glucocorticoids, and treated toxic multinodular goitre. Following a traumatic T11 fracture and significant osteoporosis risk factors (female, postmenopausal, T2DM, glucocorticoid-use, sarcoidosis, and previous thyrotoxicosis), she was started on bisphosphonate therapy in 2012 with good concordance. Bone densitometry at the time demonstrated lumbar *T*-score −1.9 and femoral neck *T*-score of −1.2.
In July 2016, she sustained the first of two notable femoral fractures in quick succession: left subtrochanteric (2016) and right subtrochanteric (2017), and was looked after by the orthopaedic team. Both of these fractures were sustained following falls from standing height (i.e. fragility fractures) and were compatible with additional classical features of atypical femoral fractures (AFF), (e.g. transverse, subtrochanteric, medial cortical spike). Critically, there was the radiological appearance of an impending AFF on the right when she first presented with the left AFF highlighting the need to closely examine the contralateral side after an AFF.
Bisphosphonates are widely used agents for both primary and secondary prevention of fragility fractures. Despite proving effective, prolonged use (median 7 years) of bisphosphonates may lead to AFFs predominantly due to suppression of bone remodelling. This has prompted several position statements to consider a bisphosphonate "drug holiday" in selected patients after 5 years of oral bisphosphonate use. However in this case, the patient had only been taking bisphosphonates for 4 years, but had significant additional risks for atypical fracture including glucocorticoid use. Therefore, this case highlights that in patients with increased risk of fracture, AFFs may occur earlier than the 5-year recommended duration of bisphosphonate therapy. Furthermore, this is one of a handful of reports of bilateral AFFs and so stresses the need to examine the contralateral femur after an AFF and work closer with our orthopaedic colleagues.

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P067

Playing tennis with off the chart Calcium levels !!

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Severe Hypercalcaemia can present as a life threatening emergency requiring urgent measures to lower the calcium. Usually, this is associated with Primary Hyperparathyroidism. It can result in obtundation, oliguria, anuria, collapse or arrhythmias. It is important to act fast and decisively to prevent fatal complications.
We describe a 39 year old gentleman who was a tennis coach, who was brought after he collapsed in his bathroom. He had a 3-month history of lethargy, dry cough, light headedness and a stone of weight loss but able to work and in fact had done tennis lessons till the previous day. He also had a week's history of increasing lethargy, anorexia, and several fainting episodes. He had no past medical problems and was not on any regular medications or over the counter supplements.
On examination, he was alert but appeared dehydrated. His veinous gas showed a high ionized calcium and the lab confirmed a very high calcium level of 4.82. His Parathyroid hormone level was off the scale at >250 pmol/l.
He was admitted to ITU and received IV Fluids, Bisphosphonate, and calcitonin for 48 hours. But the calcium was still high and he underwent haemofiltration (Continuous Veino-Veinous Hemofiltration) and Cinacalcet was introduced. He had an urgent ultrasound of his neck which showed a large right parathyroid gland. He had emergency 3 glands parathyroidectomy on day 4.
He became profoundly hypocalcaemic after surgery and needed regular IV calcium top ups despite being on good doses of alfacalcidol and oral calcium to alleviate hypocalcaemic symptoms. He went home with some element of kidney damage.
This case highlights aggressive and early measures to reduce calcium and good supportive care in a controlled environment will result in good patient outcomes.

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Clinical Biochemistry

P181

Personalized medicine and endocrine disorders: the challenges of interpreting genetic variants

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Introduction
Genetic projects, such as 100KGenomes, are identifying a vast amount of genetic variants that require interpretation. Several variants lack sufficient evidence to be classified as neutral or damaging. Such variants are annotated as 'unclassified' and interpretation of their biological effect is of paramount importance, but remains a major challenge. Variant predictors are widely used to prioritize variants for further studies. However, they report a damaging effect for a large proportion of neutral variants, thus, limiting their utility in assessing unclassified variants.
We performed a systematic analysis of unclassified missense variants in genes causing endocrine disorders and assessed the contribution of protein structure analysis to their interpretation.
Methods
We examined 383,655 missense variants annotated in ClinVar and Uniprot. Genes causing endocrine neoplasias and disorders were identified by automatically mapping OMIM entries to the ICD-10 catalog. Variant effect predictions were obtained from PolyPhen2, SIFT and MutationAssessor. Experimental protein structures were obtained from ProteinDataBank and analysed for disruption of physico-chemical features.
Results
We identified 641 genes and 11,734 variants (damaging = 6,171(52.6%), neutral = 1,473(12.5%), unclassified = 4,090(34.9%)). 1,494(36.5%) unclassified variants distributed in 118 genes could be mapped onto protein 3Dstructures.
1,498 variants were predicted damaging: 564(37.6%) were structurally analysed and 141(25%) confirmed damaging. 1,109 variants were predicted neutral: 319(28.7%) were structurally analysed and 297(93%) confirmed neutral. 711 variants were predicted damaging by two-out-of-three predictors: 258(36.2%) were structurally analysed and 40(15%) confirmed damaging. 694 variants were predicted neutral by two-out-of-three predictors: 216(31.1%) were structurally analysed and 190(88.0%) confirmed neutral. In 78 variants, results were available from only two predictors and were contradictory: 26(33.3%) were structurally analysed and a deleterious effect confirmed in 9.
Conclusion
Evidence of damage in protein structural stability provide strong evidence of a variant deleterious effect and can greatly help to prioritize genetic variations for further in vitro studies in patients with endocrine disorders.

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P182

Clinical evaluation of a multiple-gene sequencing panel for hypoparathyroidism

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Hypoparathyroidism may occur as: a hereditary syndromic disorder (e.g. Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dystrophy (APECED), Hypoparathyroidism Sensorineural Deafness and Renal Disease (HDR), Autosomal Dominant Hypoparathyroidism type 1 (ADH1), or ADH type 2 (ADH2), which are due to mutations of autoimmune regulator (*AIRE*), GATA binding protein 3 (*GATA3*), calcium-sensing receptor (*CASR*) and G-protein subunit alpha 11 (*GNA11*)); or a non-syndromic isolated endocrinopathy, due to mutations of glial cells missing homolog 2 (*GCM2*), and parathyroid hormone (*PTH*) genes. The functions of these genes are as follows: *AIRE* encodes a transcription factor controlling immune tolerance; GATA3 is a transcription factor regulating parathyroid development; CASR is a G-protein coupled receptor (GPCR) regulating extra-cellular calcium homeostasis; G-protein subunit alpha-11 is a CaSR signalling modulator; GCM2 is a parathyroid-specific transcription factor regulating development; and PTH is a regulator of extracellular calcium homeostasis. Identifying the genetic cause may facilitate the diagnosis and screening for associated endocrine and non-endocrine disorders, and genetic counselling. Historically, individual genes were screened in order of their frequencies of occurrence. However, in our experience, sequential testing of multiple genes, which was often required, can result in a delay in diagnosis and multiple patient-healthcare encounters. We have therefore evaluated the use of a panel of 6 genes: *AIRE*, *GATA3*, *CASR*, *GNA11*, *GCM2* and *PTH*, implicated in hypoparathyroidism. Gene panel testing was undertaken on 63 unrelated patients and ~40% of these had abnormalities comprising mutations ($n = 22$) and unknown variants ($n = 4$). Of the 22 mutations, 36% ($n = 8$), 23% ($n = 5$), 18% ($n = 4$), 14% ($n = 3$), 5% ($n = 1$) and 5% ($n = 1$) had mutations in *CASR*, *GNA11*, *GCM2*, *AIRE*, *PTH* and *GATA3* respectively; the frequencies involving each of the genes were not significantly different (χ^2-test). This demonstrates the utility of panel gene testing over individual gene testing to provide rapid clinical diagnoses that will benefit patients, clinicians and healthcare services.

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P183

The free androgen index in women is inaccurate when the SHBG concentration is low

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Introduction
Current clinical practice guidelines recognise that a calculated free testosterone (T) level is the single most-useful, clinically sensitive marker of androgen excess in women, but there is no clear guidance as to the best way to measure free T. Several equations have been proposed to calculate clinically useful estimates of free T including the free androgen index (FAI) and calculated free T (cFT). The FAI is not used in men but it is still commonly used in the investigation of hyperandrogenism in women.
To our knowledge the relationship between FAI and calculated free T, at the lower extremes of SHBG concentration has not been fully investigated in women.
Methods
Serum samples from women for the investigation of hyperandrogenism ($n = 53$) were measured for T by LC-MS/MS, serum albumin and SHBG (SHBG range, 10–132 nmol/L) were measured on the Abbott Architect. Calculated free T was determined using the Vermeulen equation and the FAI was calculated.
We also recorded the FAI results from 20,124 women investigated for hyperandrogenism over a ten year period, all samples had T measured using a validated LC-MS method.
Results
The ratio between FAI and cFT was found to increase at lower concentrations of SHBG in women (< 30 nmol/L).
From a total of 20,124 results 4223 were found to have a normal T (< 1.6 nmol/L) and an SHBG at the lower end of the concentration range (< 30 nmol/L). A gradual increase in the FAI was seen in women with a normal T concentarion as the SHBG concentration decreased. The FAI varied from 5 to 40 in these women, showing an 8 fold difference in results, indicating that the FAI is unreliable at low SHBG concentrations.
Conclusion
We would recommend using cFT in women instead of the FAI because of its better agreement across all SHBG concentrations.

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P184

Interference of midodrine and desglymidodrine in a plasma metanephrines LC-MS/MS assay

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Introduction
Plasma metanephrines (PMETS) are widely used as a first-line investigation for phaeochromocytoma/paraganglioma owing to the high diagnostic sensitivity of the test. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) has become the methodology of choice for measuring PMETS due to the high analytical specificity of the technique. However, there have been recent reports of interference in LC-MS/MS PMETS assays by the α1-receptor agonist midodrine.

Methods
Potential interference of both midodrine (prodrug) and desglymidodrine (active metabolite) in our PMETS LC-MS/MS assay was investigated by spiking known concentrations of these compounds into pooled patient serum. Midodrine and desglymidodrine were added at concentrations of 0, 5, 10, 15, 20 and 25 nmol/L. Plasma normetanephrine, metanephrine and 3-methoxytyramine were measured in blank and spiked serum (5 replicate analyses).
Results
In the case of midodrine, no interference was observed for normetanephrine or 3-methoxytyramine, but there was a dose-related increase in measured metanephrine. The increase in the metanephrine signal was equivalent to around 18% of the midodrine concentration. In the case of desglymidodrine there was no interference in normetanephrine but evidence of interference in metanephrine and 3-methoxytyramine. This was equivalent to around 5% for metanephrine and 1% for 3-methoxytyramine. On examination of the chromatograms there was an obvious peak eluting immediately before metanephrine in samples spiked with desglymidodrine.
Conclusions
Midodrine and desglymidodrine cause interference in our LC-MS/MS method for PMETS, particularly for metanephrine. Although this interference should be detected through routine visual inspection of chromatograms (and results not reported where interference is suspected), this is likely dependent on desglymidodrine concentration and there is a possibility that this could go undetected in the laboratory. Users should therefore be aware that PMETS LC-MS/MS assays may suffer from interference where patients are taking midodrine. We are investigating changes to the chromatography in our assay, aiming to overcome midodrine interference.

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P185

Development of a sensitive, rapid LC-MS/MS method for detection of oxytocin in human plasma

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Oxytocin is a peptide hormone consisting of 9 amino acids, with a mass of 1007 Da. It is synthesised in the hypothalamus and secreted from the posterior pituitary. It has well known roles in lactation and uterine contraction, however it is also thought to act within the brain to influence complex social behaviours such as bonding, empathy, and trust. Recently there has been increasing interest in the potential role of oxytocin in the pathophysiology of depression and autism amongst other conditions.
Oxytocin measurement in human plasma is challenging due to low circulating concentrations. Immunoassay kits for the measurement of oxytocin are readily available, however questions remain regarding their specificity and sensitivity. We aimed to develop an LC-MS/MS method for the measurement of plasma oxytocin that would be sensitive enough to detect low ng/L concentrations of oxytocin while still being suited to routine clinical use.
An LC-MS/MS method was established using a Waters Acquity UPLC system and Xevo TQS mass spectrometer, with a BEH130 C18 column. The method was linear to at least 5000 ng/L and had a short run time of 2.1 minutes. Two methods for sample clean up prior to analysis were tested. Using solid-phase extraction we were able to detect oxytocin concentrations of 50 ng/L in spiked human plasma. Improved sensitivity was provided by using antibody-coupled magnetic beads to extract oxytocin from plasma; 25 ng/L could be detected. For comparison, samples were also analysed with a Waters ionKey MS system with a flow rate of 2.5 µL/min, however this did not further improve sensitivity.
In summary we have developed a sensitive LC-MS/MS method for analysis of oxytocin which would be suitable for clinical use. Further optimisation of the extraction protocol may enhance sensitivity. Additional testing would also be required to establish reference ranges and to determine stability of oxytocin post-sample collection.

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P186

Lodotra (delayed release prednisone) is variably absorbed, and should not be used in adrenal insufficiency

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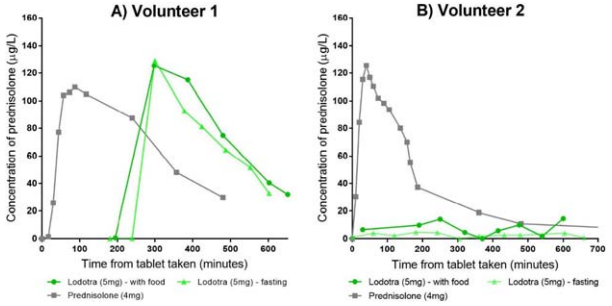
Replacing glucocorticoids in patients with adrenal insufficiency is challenging, as endogenous cortisol levels rise before waking. Currently we use steroid replacement first thing in the morning. Administration of a delayed release preparation last thing at night, if reliable, could mimic the rise in cortisol that occurs before waking. Lodotra is a modified release prednisone that has a delay in the onset of action, and when given last thing at night, might cause a rise in levels before awakening. We investigated the reliability of Lodotra absorption and conversion in the liver to prednisolone. Single doses of either standard prednisolone or Lodotra 5 mg were administered in the morning. Samples for serum prednisolone were taken at intervals.
Results
Lodotra was absorbed with a 5-h delay in one volunteer (see figure), so that if the drug is taken at bedtime (11pm), a rise on prednisolone levels would start at 0400 h, consistent with the circadian rhythm.



Lodotra was not consistently absorbed in all three volunteers. Volunteers 2 and 3 showed negligible to low levels of prednisolone absorption for a 10 hour period. Food intake did not change absorption in any of the volunteers.
Conclusion
Because of its variable absorption, we cannot recommend the use of Lodotra for primary or secondary adrenal insufficiency.

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P187

How well can we measure SHBG?

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Sex hormone binding globulin (SHBG) is a glycoprotein which binds hormones such as testosterone. Around 97% of circulating testosterone is bound to SHBG and is therefore biologically unavailable; approximately 2–3% of testosterone is free or loosely bound to proteins such as albumin, and is biologically active, or bioavailable. Free testosterone is very technically challenging to quantify; in order to circumvent this problem, equations are used to estimate free testosterone, as recommended by the British Society for Sexual Medicine. Much work has been done to standardise testosterone analysis, including production of certified reference materials and reference measurement procedures, but such attention has not been paid to the other analytes used in calculated free testosterone equations such as SHBG. We decided to compare SHBG results obtained from the 5 most

common SHBG assays found in clinical laboratories in the UK (Abbott Architect, Roche, Beckman, Siemens Immulite and Siemens Centaur) to investigate the difference in results obtained from the different methods and assess how these differences could impact on calculated free testosterone by the Vermeulen equation and also free androgen index (FAI) in females.
Anonymised surplus serum samples (40 male, 40 female) were analysed for SHBG by the five different methods. Sample aliquots were frozen at −80°C and kept frozen until analysis. Paired *t*-tests were carried out for all permutations of assays and results were found to be significantly different ($P<0.05$). The comparison between the Roche and Siemens Centaur assay showed a greater difference in the male results ($P<0.001$) than the female samples ($P<0.05$). Differences in SHBG had more of an effect on FAI than on the Vermeulen equation. These differences found in SHBG analysis, combined with any variations in testosterone and albumin measurement, could impact on clinical decisions.

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P188

The state of glutathione system in patients with type 2 diabetes

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Introduction
Glutathione system prevents oxidative stress development in erythrocites. When this system becomes depressed it predisposes a cell to apoptosis.
Aim
To study glutathione system status in patients with diabetes
Materials and methods
Included patients were divided into four groups: group 1–41 almost healthy person (control group), group 2–41 patients with type 2 diabetes (T2D), group 3–40 patients with T2D and coronary heart disease (CHD) and group 4–88 patients with CHD. Activities of glutathione peroxidase (GP, mmol/min) and glutathione reductase (GR, mmol/min) and concentrations of reduced glutathione (GSH, mmol/l), oxidized glutathione (GSSG, mmol/l) and redox-status (GSH/GSSG) were measured. A1c level was <7.5%, patients with anemia and acute cardiovascular diseases were excluded.
Results
Activities of GP, GR and concentrations of GSH, GSSG and redox-status of glutathione system presented in Table 1. GP activity was increased statistically significant in patients with T2D and T2D and CHD ($P<0.05$) and GR activity was increased in patients with CHD ($P<0.05$) compared to control group. Concentrations of GSH was decreased in groups 2 and 3 ($P<0.05$) conpared to almost healthy persons. But concentration of GSSG was significantly higher only in patients with T2D and CHD. Also CHD was associated with depression of redox-status with maximum decrease when T2D is associated with CHD.
Conclusion
T2D was associated with increased activity of GP. Decreased concentration of GSSG, increased concentration of GSH and depressed redox-status of glutathione system can be used as additional markers for early prognosis of atherosclerosis development in patients with T2D.

Table 1 Activities of GP, GR and concentrations of GSH, GSSG and redox-status of glutathione system (Me (LQ;UQ)

Findings	Group 1	Group 2	Group 3	Group 4
GP	44.97 (36.96;58.70)	51.01 (31,36;67,52)	60.13 (50,25;70,12)	45.58 (36.73;52.32)
GR	0.89 (0.69;1.10)	0.84 (0.76;1.18)	1.12 (0,81;1,28)	1.47 (1.32;1.88)
GSH	2.14 (1.98;4.19)	2.08 (2.00;2.92)	1.34 (0.61;1.41)	1,47 (1.32;1.88)
GSSG	0,33 (0.31;0.36)	0,31 (0.30;0.32)	0.40 (0.36;0.40)	0.36 (0.33;0.38)
GSH/ GSSG	6.48 (6.38;11.64)	6.70 (6.67;9.12)	3.35 (1.69;3.53)	4.08 (4.00;4.95)

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P189

Diagnosis and management of hyponatraemia in patients with cancer

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Background
Hyponatraemia (most commonly secondary to SIADH) is very common in cancer patients; it is associated with delays to oncology treatment and mortality.
Aim
To evaluate the number of patients with hyponatraemia at a tertiary referral cancer centre and assess adherence to national recommendations for investigations and treatment.
Methods
All biochemistry results (in-patient and outpatient) analysed at the Christie in September 2016 were screened for new-onset hyponatremia (serum Na <135 mmol/L). A structured checklist was used to extract data from laboratory results and patient records.
Results
552 patients had a serum Na<135 mmol/L ($n=108$, Na<130 mmol/L). We studied 91 patients (47% female, mean age 66±11 yrs, 52% outpatients) with new onset hyponatraemia <130 mmol/L ($n=19$ Na<125 mmol/L) with lung (19%), GI (22%) and gynaecological (15%) malignancies being most frequent. Paired urine and serum osmolalities and urinary sodium were tested in only 19% of the study population (Na<125 mmol/l: 63%). Thyroid function and 9 am cortisol were checked in 20% (Na<125 mmol/l: 50%). Only 11% had all investigations performed within 24 hrs (Na<125 mmol/l: 50%). From a subcohort of 63 patients, fluid status, diagnosis, treatment plan and medication review was identified in 27%, 20%, 19% and 22.5% respectively and 15.9% ($n=10$) were referred to endocrinology (9 out of 10 had Na<125 mmol/l). 6-month mortality: 43% (Na<130 mmol/L) and 57% (Na<125 mmol/L).
Conclusion
>500 patients/month at a tertiary cancer centre have hyponatraemia. Only 11% of the evaluated patients with Na <130 mmol/l (Na <125 mmol/l: 50%) patients had complete investigations (paired serum and urine osmolalities, urinary sodium, TSH and cortisol). This does not compare favourably with recent global data (21.5% compliance in cancer subgroup of hyponatremia registry). Further work is required to establish efficient and safe pathways to investigate and manage these large numbers of hyponatremic patients and identify those who will benefit from treatment to prevent delays in chemotherapy.

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P190

An unusual case of Gynaecomastia from hCG secreting bladder cancer

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A 71 year old man presented with 6 months history of pain over the nipples, weight loss of ½ stone over the previous month and nausea. Initial investigations carried out by the breast surgeons including ultrasound scan of the breast and testes were normal. He was then referred to the Endocrine department for further investigations. There was no significant past medical history, he was taking over the counter vitamins and antihistamines. Clinical examination revealed bilateral gynaecomastia with diffuse breast plates, no lymphadenopathy or organomegaly. Further investigations showed a very high hCG of 679 IU/L (0–5), FSH <0.3 u/L LH <0.3 u/L, total Testosterone 14.7 nmol/L (10–35), SHBG 64 nmol/L (10–70), Free testosterone 280 pmol/L (225–9999), 17 Oestradiol 236 pmol/L, Prolactin 148 mu/L, PSA 2.8 ug/L, Alpha fetoprotein 2.3 kU/L (0–10), TSH 0.81 mu/L.
CT scan showed a large right sided bladder tumour extending beyond bladder with gross hydronephrosis on right and metastatic lesions in the lung. Biopsy confirmed a T4NxM1 sarcomatoid bladder tumour. He was commenced on palliative Gemcitabine and Carboplatin and subsequently died.
Discussion
This is an unusual case of βhcG secreting bladder tumour leading to gynaecomastia. A literature search has only shown 5 previous reported cases. Bladder cancers have been shown to have receptors for βhcG and the ectopic production of βhcG contributes to the radio-resistance and metastatic potential of

such secreting tumours through inhibition of apoptosis. βhcG can be used as a prognostic marker. Patients with high βhcG have a higher grade of malignancy and poor histological differentiation in addition to less favourable survival outcomes.

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P191

An audit of the management of patients presenting with hyponatraemia

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Introduction
Hyponatraemia is the most common electrolyte disturbance, affecting 15–20% of emergency admissions to hospital. It is associated with increased mortality and length of stay in hospital. This audit was performed to evaluate how well hyponatraemia is being investigated and managed in the Acute Assessment Unit (AAU).
Methods
Sodium level on admission for all patients attending AAU at Conquest Hospital over a 1-month period was recorded from computer records. The notes of 30 patients with hyponatraemia on admission were studied and NICE recommendations were used for comparison. These state that paired serum osmolalities, urinary sodium, thyroid function tests and serum cortisol should be performed. The advised management steps include fluid restriction/hypertonic saline and stopping causative medications. The average length of stay, re-admission rates and mortality rates, from July-November 2016 (time of audit), were recorded.
Results
71 patients of the 481 patients admitted to AAU in July 2016 had hyponatraemia on initial blood test (16.2%). Of the 30 hyponatraemic patients studied, 46.7% of had hyponatraemia documented as a problem in their notes. 56.7% had their fluid status assessed and 20% had one or more of the recommended investigations performed. 23% had one or more of the recommended management steps documented in the plan. The average length of stay of this group of patients was 10 days, compared with the national average of 5 days in 2015–2016. Re-admission rates were 33.3% and mortality rates 18.5%
Conclusion
It is evident that hyponatraemia is not being consistently recognised as a problem and is insufficiently investigated and managed. Given the morbidity and mortality associated with hyponatraemia and the variety of underlying causes, it is imperative that changes are made to improve care. We have produced guidelines locally and plan to re-audit following implementation of these.

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P193

The investigation of hyponatraemia in hospitalised patients: an audit

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Introduction
Hyponatraemia is the commonest electrolyte disturbance affecting patients in and out of hospital. Streamlining and improving the investigation of hyponatraemia will quicken diagnosis, improve patient outcomes and prevent deterioration and unnecessary stay in hospital. We aimed to audit the assessment of patients with hyponatraemia against our existing guidelines (Hyponatraemia – An Investigator's Checklist).
Method
This was a retrospective audit looking at patient-admissions with a diagnosis of hyponatraemia on their discharge-summary within a 1-year period (March 2014 to March 2015). There were 80 cases in total. As well as demographics we assessed notes for assessment of severity and onset, clinical assessment of volume status, assessment of paired serum-urine osmolality and sodium, review of medications and documentation of a probable cause for hyponatraemia.
Results
We retrieved notes of 56 patients (41 were female). Average age (range) for the group was 80 (55–96) years and median length of hospital stay was 5 days. Their average sodium level was 122 mmol/l and 50% had severe hyponatraemia ($<$125 mmol/l). The onset of hyponatraemia was equally distributed amongst acute, subacute and chronic. Assessment of severity and onset was done for 100% of patients; clinical assessment of volume status was done for 18% of patients; assessment of paired serum-urine osmolality and sodium was done for 63% of patients; a review of medications was done for 64% of patients and a probable cause was found for 78% of patients. Patients had other investigations (e.g., endocrinology, imaging, etc.) depending on initial assessments.
Conclusions
This audit demonstrated partial-substantial adherence to guidelines for most of the initial assessment steps during the investigation of hyponatraemia, apart from clinical assessment of volume status. As an action plan, an automatic reminder of the guidelines appears the system for moderate-severe hyponatraemia when checking for biochemistry results. A re-audit is planned for 3 years afterwards.

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P194

A well recognised but forgotten cause of undetectable Magnesium

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A 74 years old man prsented with gradually worsening confusion with associated jerky movements with background of well controlled type 2 Diabetes, CKD-3, IHD and previous duodenal ulcer. His was on Finasteride, Omeprazole, Mirtazapine, Tamsulocin, Metformin, Atorvastatin, Humulin I insulin. He was taking omeprazole for Duodenal ulcer since 1993.
On examination he had jerky movements of the arms suggestive of muscles spasms. Rest of the examination was unremarkable.
He was found to have Hypocalcemia of 1.63 mmol/L (NR 2.20–2.60) with inapproiately normal PTH of 6.6 pmol/L (NR 1.6–7.2). Serum potassium was normal. Furthur investigation into hypocalcemia revealed an undetectable Magnesium which was felt to be the likely cause of his Hypocalcemia. Serum Vitamin D level were low at 15 nmol/L (NR $>$30). 24 hours urinary Magnesium was normal at 3.4 mmol (NR 2.4–6.5) which confirmed that there was no renal Magnesium loss.
ECG showed prolongation of the QTc (460 ms) with prolonged PR interval consistent with Hypomagnesemia.
He was treated with intravenous Magnesium and oral supplements and both Mg and Calcium were normalised. PPI was replaced with H2 blockers.
This gentleman had severe symptomatic hypomagnesaemia with undetectable Mg levels secondary to chronic PPI therapy.
PPIs impairs the active transport of magnesium in intestinal epithelial cells by inhibition of transient receptor potential melastatin 6(TRPM6) and TRPM7 channels. This is thought to be related to the changes in intestinal pH caused by Proton pump inhibitors. Hypocalcemia is a frequent associated finding as hypomagnesemia causes a degree of hypoparathyroidism by inhibiting the release of PTH from parathyroid gland as well as causing PTH resistance in bones.
Physicians need to have high index of suspicion to detect Hypomagnesaemia as it is not routinely checked, particularly patients on long term PPI therapy and Diuretics as advised by FDA and MHRA to avoid life threatening Cardiovascular and neurological sequelae.Unexplained hypocalcaemia and Hypokalemia particularly if refractory to treatment also warrants checking Magnesium levels.

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Diabetes and Cardiovascular

P201

Magnesium modulates the expression of INSR and GLUT4 in streptozotocin-nicotinamide-induced type-2 diabetic rats

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Glucose uptake is mediated by a family of glucose transport proteins, which are known to be expressed in specific insulin-sensitive tissues. Magnesium (Mg) is essential for autophosrylation of insulin receptor (INSR) and translocation of glucose transporter 4 (GLUT4) to the plasma membrane to facilitate glucose homeostasis. The specific effect of magnesium on INSR and GLUT4 expression in a diabetic state is however lacking. We conducted this study to investigate

whether magnesium supplementation alters INSR and GLUT4 expression in the insulin-responsive skeletal muscle, and whether this contributes to improved glucose homeostasis in type 2 diabetic (T2D) rats.
Thirty-two (32) male Sprague-Dawley rats were randomly divided into four groups consisting of control, diabetic untreated (DU), diabetic treated with 1 mg of Mg/kg diet (Mg1-D) and diabetic rats treated with 2 mg of Mg/kg diet (Mg2-D). T2D was induced with a single intraperitoneal (i.P) injection of nicotinamide (120 mg/kg BW) and streptozotocin (55 mg/kg BW). Animals with blood glucose level above 200 mg/dl were considered to be diabetic. Glucose and insulin tolerance tests, lipid and oxidative parameters as well as expression of INSR and GLUT4 were determined in all experimental rats. The obtained data was analyzed by GraphPad Prism (v. 5) using One-way analysis of variance (ANOVA).
Diabetes resulted in impaired glucose tolerance and insulin resistance. Mg supplementation in diabetic rats however improved glucose tolerance with increased insulin sensitivity. Fasting glucose, cholesterol, triglyceride, high density lipoprotein (HDL) levels as well as HOMA-IR were significantly increased in diabetic rats (DU vs CTR); these were however normalized to near control values by Mg supplementation. In addition, Mg treatment attenuated the diabetes-induced decrease in the expression of INSR and GLUT4 receptors in the gastrocnemius muscle of the diabetic rats.
This study demonstrates that Mg decreases the metabolic disturbance associated with T2D, improving glucose/insulin metabolism through an increased expression of INSR and GLUT4 receptors.

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P202

Selective expresssion of one specific isoform of the coxsackie adenovirus receptor (CAR) in the human pancreatic beta cells

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Aims and Objective
A transmembrane cell-adhesion protein, the Coxsackie-adenovirus receptor (CAR) serves as an entry receptor for enteroviruses and may be essential for their ability to infect cells. Since beta-cell enteroviral infection could contribute to the development of Type 1 diabetes, it is important that CAR expression is analysed in the human pancreas. CAR exists as at least 5 isoforms and we have studied the expression of these different isoforms in human pancreas.
Methods
Formalin-fixed paraffin embedded pancreatic sections from 17 non-diabetic controls, and 6 Type 1 diabetes patients were studied, together with a human tissue microarray. Immunohistochemistry, confocal immunofluorescence microscopy and western blotting with isoform-specific antisera were employed to examine the expression and cellular localisation of each CAR isoform. Isoform specific qRT-PCR was performed on RNA extracted from isolated human islets.
Results
An isoform of CAR having a terminal SIV motif and a unique PDZ binding domain was preferentially expressed in human beta cells at the protein level. This was also the major isoform amplified by RT-PCR from RNA extracted from isolated human islets. Surprisingly, this protein was distributed mainly within the cytoplasm of beta cells whereas it was primarily localised to the plasma membrane in tissues such as testis and bladder. Co-immunofluorescence analysis revealed significant subcellular co-localisation with ZnT8, PC1/3 and insulin, but not with pro-insulin, in beta-cells.
Conclusion
The restricted expression of the SIV protein may contribute to the selective infection of beta cells by enteroviruses under conditions when it is translocated to the cell surface.

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P203

Induced maturity affects normal beta cell function

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Aim: One of the hallmarks of type 2 diabetes (T2D) is impaired beta cell function, which develops in part as a result of widespread cellular de-differentiation. The current state-of-the-art defines beta cells as a heterogeneous islet population, with the existence of individual subpopulations including specialised 'pacemakers'. We sought here to understand how overexpression-induced beta cell maturity affects such heterogeneity, before examining the influence of this on islet function and insulin secretion.
Materials and methods
An adenoviral polycistronic construct for *Ngn3*, *MafA*, *Pdx1* and *mCherry* (Ad3-NPM) was used for inducing overexpression in adult mouse islets. PATagRFP- or non-transduced (CT) islets served as controls. Gene expression was quantified by qRT-PCR. *Pdx1* and insulin content was analysed by immunohistochemistry using a Zeiss LSM780 confocal microscope. Nipkow spinning disk microscopy was used for quantifying Ca^{++}, ATP and cAMP dynamics in live islets. Glucose-stimulated (GSIS) and incretin-stimulated insulin secretion (ISIS) were assessed by HTRF assay.
Results
Ad3-NPM treatment increased *Pdx1* and *MafA* expression in mouse islets, while *Ngn3* levels remained unchanged. Immunohistochemistry showed that *Pdx1* overexpression preferentially occurred in immature beta cells, inducing cellular homogeneity. Ca^{++} levels showed a marked decrease ($\Delta F = 0.81$ in CT vs 0.44 AU in Ad3-NPM-islets; $P < 0.01$), accompanied by reduced beta cell-beta cell coordination and a reduced number of beta cell pacemakers, *i.e.* hubs (12.6 *vs* 5.6% hubs, CT vs Ad3-NPM; $P < 0.05$). The ATP/ADP ratio was slightly higher in Ad3-NPM-transduced islets, although cAMP responses to glucose were sharply reduced. Basal insulin release was increased following overexpression, with impairments in both GSIS and ISIS (7.5-fold *vs* 5-fold after glucose stimulation and 98-fold vs 50-fold after exendin-4 stimulation; CT vs Ad3-NPM-islets).
Summary
Induced beta cell maturity leads to islet failure and lowered insulin secretory capacity. This work underlines the importance of maintaining subtle differences in beta cell maturity for normal islet function.

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P204

Effect of vitamin B12 deficiency on the lipid lowering effect of metformin in the liver

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Background
Metformin is currently the first drug of choice for treatment of type 2 diabetes (T2D). Metformin is known to reduce lipid levels through activation of AMP activated protein kinase-alpha (AMPKα). Metformin induces deficiency of vitamin B12 (B12) in patients with T2D. In humans, studies have shown that low B12 is associated with dyslipidemia (higher triglycerides and low HDL). Therefore, we investigated whether B12 deficiency may impair metformin action from achieving the desired lipid lowering effect in the liver.
Methods
Hep G2 cell line was cultured using custom made B12 deficient Eagle's Minimal Essential Medium (EMEM) and seeded in four different concentrations of B12 media such as 500 nM (control), 1000 pM, 100 pM and 25 pM (low) B12 until 100% confluence was achieved. The cells were exposed to 24 hour treatment with 1 mM and 2 mM metformin before harvest. Protein and gene expressions were characterized using western blotting and real time PCR (qRT-PCR) respectively.
Results
Low B12 (25pM) in HepG2 cell line decreased levels of AMPKα and its downstream target pACC, compared to control. Administration of increasing concentrations of metformin (1 mM and 2 mM) to low B12 hepatocytes significantly impaired the upregulation of pAMPKα and pACC. In addition, we found that downregulation of nuclear transcriptional factor sterol regulatory element binding protein (SREBF1)

and the genes involved in hepatic *de novo* fatty acid synthesis pathway, [fatty acid synthase (FASN), acetyl coenzyme A carboxylase (ACC) and elongation-of very-long-chain fatty acid (ELOVL6)] and TG biosynthesis [glycerol-3-phosphate acyltransferase (GPAT) and diacylglycerol acyl transferase 2 (DGAT2)] were significantly impaired in low B12 cells treated with metformin.
Conclusion
Our study provides novel evidence that Vitamin B12 deficiency (1) lowers levels of pAMPKα and pACC, and (2) metformin administration in low B12 hepatocytes failed to restore the levels of pAMPKα and pACC, and the genes involved in lipid metabolism. The mechanisms involving regulation via AMPK requires further studies.

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P205

The effect of escalating doses of beta-blockers and ACE inhibitors on mortality in patients with heart failure and diabetes mellitus

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Introduction
Diabetes mellitus (DM) is a common co-morbidity in patients with heart failure and reduced left ventricular ejection fraction (HF-REF), and is associated with adverse prognosis. Subgroup analyses of randomized controlled trials suggest patients with DM benefit prognostically from beta-adrenoreceptor blockers (BB) and angiotensin converting enzyme inhibitors (ACEi). However, it remains unclear whether escalating doses of these agents are associated with similar benefit in people with DM.
Hypothesis
Escalating doses of BB and ACEi are associated with similar mortality reduction in HF-REF patients with and without DM.
Methods
Prospective cohort study of 1802 patients with stable HF-REF, recruited from 4 UK hospital clinics between 2006 and 2014. Mortality data was available in all patients after a mean 4-year follow-up period. Prescribed BB dose was expressed as the equivalent daily dose of bisoprolol, and ACEi dose as the equivalent daily dose of ramipril. Cox regression analysis was used to define the interaction between DM and BB or ACEi dose.
Results
28% of patients had DM; they received similar doses of BB and ACEi to patients without DM, and had comparable resting heart rate. Every milligram increment in BB dose was associated with a 3.5% (95% CI 0.7–6.3%; $P=0.015$) reduction in mortality in patients without DM, and an 8.9% (95% CI 5–12.6%; $P<0.001$) reduction in patients with DM (interaction $P=0.027$). This interaction persisted in multivariate regression analysis accounting for other prognostically important factors. A similar interaction was in analyses restricted to progressive heart failure death, or sudden cardiac death. Whilst rising ACEi dose was also associated with lower mortality, no interaction with DM status was found.
Conclusion
Escalating BB, but not ACEi, dose is associated with greater all-cause and mode-specific reductions in mortality in patients with DM.

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P206

The impact of a dedicated metabolic hepatology clinic for the treatment of non-alcoholic fatty liver disease

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Introduction
Non-Alcoholic Fatty Liver Disease (NAFLD) is the hepatic manifestation of metabolic syndrome and is tightly associated with insulin resistance and type 2 diabetes (T2DM), both risk factors for disease progression, liver failure and cardiovascular complications. A multidisciplinary approach involving hepatologists and diabetologists working alongside allied health professionals is thus advocated for the management of NAFLD. Interventions delivered include dietary and lifestyle advice as well as pharmacological interventions for cardiovascular disease and diabetes. Objective evaluation of this multidisciplinary intervention on liver and cardio-metabolic health is currently limited.
Objective
This retrospective study aimed to determine the impact of a large tertiary multidisciplinary NAFLD clinic on liver and cardiovascular disease risk factors using both clinical and surrogate markers of metabolic syndrome, cardiovascular risk and liver disease between 2014-17.
Results
186 patients with NAFLD and without other hepatic co-morbidities were followed from referral until their latest review. Patients were followed for a median of 13.5 months (2–35). 30% had confirmed liver cirrhosis and 60% had T2DM at baseline. Median alanine aminotransferase (ALT) fell significantly (50IU/l to 39IU/l; −22%, $P<0.0001$) from baseline to follow-up. Similarly, median weight reduced significantly by 3.9 kg (−3.9%, $P<0.0001$), as did total cholesterol (−0.6 mmol/l; −11.8%, $P=0.0092$). Median HbA1c fell 4 mmol/mol (−4.2%, $P=0.0009$) in the total cohort; reduction was most marked in patients with poorly controlled diabetes (HbA1c >58 mmol/mol at baseline: −14.5 mmol/mol; −19.0%, $P<0.0001$). Median liver stiffness measured using transient elastography, a non-invasive measure of liver fibrosis, showed a significant reduction of 1.9 kPa (−20%, P=0.0069).
Conclusion
Our results demonstrate that patients managed through a multidisciplinary metabolic hepatology clinic exhibit significant improvements in measures of liver and cardio-metabolic health. Patients with poorly controlled T2DM, who may be at greatest risk of liver disease progression, demonstrated the largest improvement in HbA1c of 14.5 mml/mol (>1%HbA1c), a reduction well known to reduce diabetes complications. This may potentially also confer good benefit in slowing NAFLD progression.

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P207

The impact of a dedicated metabolic hepatology clinic for the treatment of non-alcoholic fatty liver disease

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Abstract withdrawn.

P208

Do glucocorticoids cause mitochondrial substrate switching in fetal cardiomyocytes?

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Background
During fetal development, the heart switches substrate preference from glucose to fatty acids, such that in the adult heart, 50–70% of ATP is derived from fatty acid oxidation. What triggers this switch is currently unclear. *In vivo*, the late gestation rise in glucocorticoid levels is essential for structural and functional maturation of the fetal heart. Glucocorticoid treatment of fetal cardiomyocytes induces

expression of PGC1a (a master regulator of mitochondrial phenotype), lipin1 and KLF15 (genes involved in fatty acid oxidation). We hypothesized that glucocorticoids instigate the switch to fatty acid oxidation in late gestation fetal cardiomyocytes.
Methods
Primary fetal cardiomyocytes were isolated following collagenase and pancreatin digestion of embryonic day (E)14.5–15.5 hearts. After 2 days in culture, cells were treated for 24 h with 1 mM dexamethasone. Oxygen consumption rate (a measure of mitochondrial respiration) and acidification rate (a measure of glycolysis) were measured using a Seahorse XF24 Analyzer using mitochondrial stress tests and glycolysis stress tests as appropriate. Respiration was measured in the presence of the fatty acid, palmitate (100 mM) and the fatty acid uptake blocker etomoxir (6 mM) or vehicle.
Results
Dexamethasone treatment did not alter glycolysis. Leak respiration was increased in dexamethasone treated cells (64.2 ± 8.2 versus 82.02 ± 14.25 pmol/min/protein, mean ± SD, $n = 8$). In palmitate-treated cells, dexamethasone increased basal respiration rate (517.9 ± 48.0 versus 366.7 ± 71 pmol/min/protein, mean ± SD, $n = 5$) and oxygen consumption (related to ATP production, 159.5 ± 62.8 versus 297.9 ± 35.5 pmol/min/protein, mean ± SD, $n = 5$) compared to vehicle. Etomoxir inhibited these dexamethasone-dependent increases.
Conclusion
These data support a glucocorticoid-induced switch in substrate preference towards fatty acid oxidation in fetal cardiomyocytes. The dexamethasone-induced increase in proton leak may serve to minimize DNA damage caused by mitochondrial reactive oxygen species (ROS) production, a mechanism that contributes to cardiomyocyte maturation. Future experiments will investigate whether glucocorticoids enhance mitochondrial ROS production.

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P209

Assessment of glycated haemoglobin among HIV patients pre and post highly active antiretroviral therapy (HAART) in Kano, Northwestern Nigeria

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Background
The exposure to HAART has increased the chances of developing Diabetes among HIV patients. Hyperglycaemia is more common among those on Protease inhibitors (PI)-based regimens compared to other regimens. Glycated hemoglobin (HbA1c) is now being recommended by the American Diabetes Association (ADA) for the screening of Diabetes because of convenience as it does not require fasting.
Objective
We aimed to determine the change in glycated hemoglobin after the commencement of HAART and the factors associated with this change.
Methodology
It was a longitudinal prospective study. One hundred and eighty HIV patients that met HAART criteria were recruited before the commencement of therapy. Their HbA1c and other anthropometric parameters were measured. Six months into HAART, the HbA1c, and other indices were repeated. Only data of 150 participants were available at the end of the study.
Results
The mean age of the participants was 35.7 ± 10.0 years, and 64% of them were females. The mean pre-HAART HbA1c was 4.2 ± 0.7% while the post-HAART HbA1c was 4.8 ± 1.3% with a statistically significant difference ($P = 0.000$). Based on the ADA criteria for screening of Diabetes and Prediabetes in asymptomatic adults using HbA1c, 97.4% of the participants were normal, 1.3% in the Prediabetes range and 1.3% were in the Diabetes range also. Following HAART exposure, 87.3% were found to be normal, 4.7% were in the Prediabetes range while 8% were in the Diabetes scale ($P = 0.005$). The factors that were discovered to be associated with the development of Prediabetes or Diabetes among the study participants following HAART include age more than 40 years, longer duration of HIV infection and HAART, exposure to PI-based regimen, increase body mass index and increase waist circumference ($P < 0.05$).
Conclusion
Exposure to HAART particularly Protease inhibitors cause hyperglycemia and its attendant complications in HIV patients. There is the need for regular metabolic screening and follow-up among these patients, and glycated hemoglobin is useful for screening.

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P210

The effect of obesity on cardiovascular risk profile and microvascular disease in type 1 diabetes

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Background
Obesity and subsequent insulin resistance is becoming more frequent among type 1 diabetes (T1DM) patients, leading to 'double diabetes' and potentially increasing vascular risk. Studies in double diabetes remain limited and this population is not fully characterised.
Aims
To investigate the prevalence of overweight and obese T1DM patients and analyse the effects of increasing weight on cardiovascular risk and microvascular outcomes in this cohort.
Methods
Single centre observational study of 1132 T1DM patients aged 19–40. Diagnosis of microvascular disease and cardiovascular risk (lipid profile and blood pressure) were identified using patient notes. Data were analysed using regression models with adjustments for HbA1c, age, gender and duration of diabetes.
Results
Body mass index (BMI) was used to classify individuals into normal weight (NW, BMI 20–24.9 kg/m^2), overweight (OW, BMI 25–29.9 kg/m^2) and obese (OB, BMI > 30 kg/m^2), with a prevalence of 43%, 38% and 17%, respectively.
LDL-cholesterol was increased in OW and OB compared with NW (2.6 ± 0.78, 2.7 ± 0.83 and 2.4 ± 0.72 mmol/L, respectively; $P < 0.01$) with an inverse picture for HDL-cholesterol, 1.5 ± 0.56, 1.5 ± 0.54 and 1.7 ± 0.48 mmol/L, respectively; $P < 0.01$). Odds ratio for hypertension was 1.91 (CI: 1.58–2.24, $P < 0.001$) in OW and OB groups compared with NW. Significantly increased rates of retinopathy were observed in OW and OB patients compared with NW, but this difference was lost after adjustment for confounders.
Conclusion
Overweight and obese T1DM patients have pro-atherogenic lipid profile and higher blood pressure compared with normal weight patients, independent of HbA1c. These data suggest that overweight and obese T1DM patients may be at increased risk of micro- and macrovascular complications and future interventional outcome studies are warranted.

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P211

Nuclear factor-kappa beta activation and monocyte-endothelial adhesion lead to chemerin induced endothelial cell inflammation

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Chemerin, a chemoattractant protein, acts *via* a G-protein coupled chemokine receptor, *i.e.* Chemokine like Receptor 1/ChemR23; levels of which are elevated in pro-inflammatory states such as obesity and type 2 diabetes mellitus (T2DM). Obesity and T2DM patients are at high risk of developing cardiovascular disorders such as atherosclerosis. We have reported that chemerin induces human endothelial cell angiogenesis and since dysregulated angiogenesis and endothelial dysfunction are hallmarks of vascular disease; we sought to determine the effects of chemerin on monocyte-endothelial adhesion, and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), a critical pro-inflammatory transcription factor. Human endothelial cells were transfected with pNF-kappaB-Luc plasmid. Chemerin induced NF-κB activation *via* the MAPK and PI3K/Akt pathways. Western blot analyses and monocyte-endothelial adhesion assay showed that chemerin increased endothelial cell adhesion molecule expression and secretion, namely E-selectin (Endothelial Selectin), VCAM-1 (Vascular Cell Adhesion Molecule-1) and ICAM-1 (Intracellular Adhesion Molecule-1), leading to enhancement of monocyte-endothelial adhesion. Additionally, we showed a synergistic response of the pro-inflammatory mediator, Interleukin-1β with chemerin induced effects. Chemerin plays an important role in endothelial inflammation, as it induces monocyte-endothelial adhesion, a critical step in the development of atherosclerosis.

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P212

'Morning sickness in a 60 year old lady' An unusual presentation of an Insulinoma at a northen DGH.

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A 60 year old lady presented to her GP with symptoms, she described as 'morning sickness'.
She also reported nausea (better after eating), mild epigastric discomfort.
Examination revealed a soft non tender abdomen, with no organomegaly.
She was referred for urgent upper GI endoscopy and abdominal USS.
Initial bloods showed impaired liver function, with a ALT of 140 and a Alk Phos of 366.
USS - abdomen showed grossly abnormal large liver which contains multiple lesions. Possible 25 mm mass is seen on the body/tail of the pancreas.
OGD revealed inflammation of the stomach.
She was then referred urgently to the Gastroenterology Department.
CT scan showed multiple necrotic liver metastasis with tumour in the pancreas.
Alpha-fetoprotein checked on 2 occasions showed elevation and therefore possibility of hepatocellular cancer.
Liver biopsy performed initially inconclusive but Immunohistochemistry for neuroendocrine markers shows positive staining with Synaptophysin, chromograin, CD56.
Referred on to neuroendocrine Oncology clinic.
Unfortunately she was admitted acutely after suffering a life threatening hypoglycaemic episode.
Despite uptitrating doses of Diazoxide she continued to suffer recurrent hypoglycaemia and reported feeling increasingly sickly which was impairing her ability to eat.
During the admission managing her blood sugars proved difficult and at times she was on intravenous glucose. Under advice from the Neuroendocrine Oncologists; Octreotide was commenced to try and help with blood sugar control.
There was a mild improvement with the Octreotide.
Subsequent CT scans unfortunately showed significant progression in her liver metastasis within a 10 week period but interestingly her pancreatic primary was relatively unchanged.
She was transferred to our regional tertiary centre where she was commenced on a combination of Oxaliplatin and Fluorouracil.
Conclusion: A rare neuroendocrine tumour metastatic at presentation.
This case highlights the importance of multidisciplinary team working and how to provide symptomatic relief for patients suffering life limiting hyperglycaemia secondary to insulinomas.

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P213

Genomic instability in type 2 diabetes mellitus patients from Yucatan, Mexico

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Background
Genomic damage plays an important role in the pathogenesis of Type 2 Diabetes Mellitus (T2DM) and its complications. This instability increases with impaired metabolic control, and is aggravated by the presence of advance glycation-end products (AGEs) causing more cell damage. The aim of this study was to analyse the presence of genomic instability in patients with T2DM and its association with the levels of AGEs, namely glycated haemoglobin (HbA1c) and glycated albumin (GA)
Patients and methods
The study design was observational, cross-sectional, and comparative with 36 participants diagnosed with T2DM, attending an Endocrinology Service in a Regional Hospital in Yucatán, México. The main inclusion criteria were: an evolution time of the disease of at least 3 years and having been a resident of the region of at least 10 years. We included 12 healthy subjects as a control group. All volunteers were tested for plasma glucose, HbA1c, GA, and body composition. The genomic instability determination was performed by single cell gel electrophoresis ('comet' assay), using peripheral blood mononuclear cells, fluorescence microscopy and a special software for image analysis.
Results
Between 75 and 81% of the T2DM participants showed some degree of impaired metabolic control with higher levels of HbA1c, GA or both. The genomic instability showed a significant association for high degree of DNA fragmentation and T2DM participants ($P=0.032$). Correlation analysis demonstrated that higher serum GA levels had higher 'comet' length tail (indicating higher instability) when cells were exposed to oxidative stress ($P=0.024$). Among other findings, waist girth was significantly correlated with higher DNA fragmentation ($P=0.044$).
Conclusion
Although there is evidence that T2DM is associated to genomic instability, we showed that higher levels of GA are associated to a higher genomic instability, and according to some authors, this biomarker could represent a better indicator than HbA1c for metabolic impairment.

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P214

Care processes and intermediate outcomes among patients with diabetes mellitus in a tertiary hospital in Southwestern Nigeria: A retrospective review of records

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Introduction
Diabetes mellitus (DM) challenges our health systems because of its prevalence, chronicity, complications, cost and complexity of care. Auditing care processes and outcomes is needed for monitoring implementation of existing guidelines, designing interventions and tracking progress. We assessed the care processes (CP) and intermediate outcomes (IO) among patients with DM who attended the diabetes clinic of a tertiary hospital in Nigeria between 2010 and 2015.
Patients/Methods
Each patient's record was reviewed over a 24-month period. Data on selected care processes (clinic attendance, Diabetes Self-Management Education (DSME) session, clinical examination, and routine investigations) and outcomes (glycaemic control, blood pressure (BP) control, renal function and cholesterol levels) were extracted. Descriptive statistics were used to summarise the results and tests of association were done between selected variables.
Results
Among the 390 patients, 55.1% were middle-aged and 62.6% were females. Majority (92.3%) had type 2 DM while 76.4% had coexisting hypertension.
Forty-two percent of patients missed clinic appointments. Less than 5% had foot or eye examination done annually, while 32.8% and 16.4% respectively had the examinations done at least once in 24 months. All the patients had BP checks at least annually and 49% had a recent DSME session.
Urinalysis, lipid profile, estimated Glomerular Filtration Rate (eGFR) and glycated hemoglobin (HbA1c) were done at least once in 24 months in 36.4%, 48.0%, 48.9% and 49.7% of patients respectively.
Among the patients, 55% and 69% had good glycaemic control (HbA1c $<7\%$) and BP control ($<140/90$ mmHg) respectively. The proportion of subjects that had optimal eGFR, urinalysis and LDL-cholesterol were 83%, 40% and 41% respectively.
Males and young adults were more likely to miss appointments, while patients with a recent DSME were likely to have more care processes. Patients who missed appointments had poorer glycaemic control.
Conclusion
The overall receipt of recommended care processes and attainment of optimal intermediate outcomes was inadequate. There is vast room for improvement.

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P215

A clinical conundrum of euglycaemic ketoacidosis

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Case History
37 years old female, presented to Emergency department with worsening SOB over last 24 hours. On systemic enquiry, patient complained of epigastric pain

after eating and admitted to un-intentional 22 Kg weight loss in last four months. She clinically appeared dehydrated, with mild epigastric tenderness and no other abnormal signs. She denied any alcohol ingestion or illicit drug use. She had treated Vitamin B12 deficiency and idiopathic macrocytosis. Initial investigations revealed raised anion gap metabolic acidosis with PH 7.1, Serum ketones 7.0, Bicarbonate 4.8, PCO2 2.2, BE −23.4, Lactate 2.1, Blood glucose 4.6, CRP 222 and amylase 175. Urine pregnancy test was negative. She had normal thyroid function test, cortisol and a CXR.
Patient was managed as euglycaemic diabetic ketoacidosis with variable rate intravenous insulin infusion (VRIII) alongside dextrose infusion, which led to resolution of metabolic acidosis. HbA1c 33 mmol/mol, Anti-GAD, Anti-ICA and Anti TTG antibodies were negative and subsequent duodenal biopsy was normal. Patient was discharged on 4 units of levemir once daily, only to be discontinued few days later due to repeated hypoglycaemia.
Patient had readmission couple of months later with chest pain and imaging studies revealed, small/trace bilateral pleural effusion and small volume ascites. The radiological features were suggestive of chronic pancreatitis but not confirmatory.
On detailed exploration of family history, it was found that her sister is on Creon and not on insulin. Her 25 years old brother was admitted with pancreatitis and DKA, and his HbA1c was elevated at 103 mmom/mol. Her grandmother and great grandfather had diabetes.
Conslusion
In summary, three siblings with features of pancreatitis, one presented as euglycaemic diabetic ketoacidosis, second as DKA and third having exocrine pancreatic insufficiency. This raises the possibility of Familial Pancreatitis with clinical features in varying stages of disease.

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P216

The adequacy and effectiveness of inpatient diabetes referrals at University Teaching Hospital

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Introduction
According to think glucose traffic light referral, Diabetic patients with persisting hyperglycaemia or recurrent hypoglycaemia should be referred to diabetes specialist team, which include diabetic specialist nurses (DSN). In our trust, the point of care alerts the system when BM is <4 mmol/l and $>$ 20 mmol/l.
Aims and Methods
We conducted a retrospective analysis of all patients within a 2 week period at our hospital with blood sugar levels $<$ 4 mmol/l or >15 mmol/l. We looked at 397 patients in total, and evaluated the adequacy of referral to the DSN. We also looked at the current work load for DSN's, calculating the number of hours needed to see all of the referred patients. We assumed that each referral would take 30 minutes to assess. We further extrapolated the data, assuming all patients requiring referral were referred, to estimate the total number of hours needed for DSN's to see all the necessary patients.
Results
A total of 220 patients were recorded to have a BM $<$ 4.0. Of these 202 were referred to DSN's (92%). 65 Patients were recorded to have a BM >15, and only 25 of these were referred to DSN's (38%). 112 patients were recorded to have BM >20, and only 40 of these were referred to DSN's (36%). It was calculated that an average of 12.8 h each day was needed to assess patients with abnormal BMs, with the number of hours being as high as 15 on some days.
Conclusion
Currently there are an inadequate number of referrals made to DSN's in our hospital. This may be due to poor education amongst healthcare professionals, with lack of guidance regarding when to refer. In addition, despite the inadequate referral, we have highlighted the large demand for DSN's, with referrals taking a significant number of hours each day to assess. With an increasing incidence of diabetes, perhaps this is an area that needs further investment in our health-board.

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P217

Audit on management of hyperglycaemia and steroid therapy

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Introduction
We undertook an audit evaluating the glycaemic management of patients on steroids. This audit is based on the Joint British Diabetes Societies guideline on Management of Hyperglycaemia and Steroid (Glucocorticoid) Therapy, 2014.
Method
The audit was conducted prospectively over a period of 5 days. All patients on steroids greater than 5 mg of Prednisolone, or an equivalent dose of alternative synthetic glucocorticoid were included. The pilot audit was conducted on the Acute Medical Unit, Respiratory Wards and Haematology Wards at Manchester Royal Infirmary.
Results
A total of 38 patients were identified.
Types of steroids used:
Prednisolone: 34 patients
Hydrocortisone: 2 patients
Dexamethasone: 2 patients
Methylprednisolone: 2 patients
* both the patients on Methylprednisolone were subsequently changed to Prednisolone after 3 days as part of their chemotherapy regime.
The main indication for high dose steroid was for asthma/chronic obstructive pulmonary disease (COPD) exacerbation; 26/38 (68.4%). Other indications (each with 1–2 patients each) were for B Cell Lymphoma, Lung cancer, Chronic Lymphocytic Lymphoma, Graft versus Host Disease, Sarcoidosis, Vasculitis, Ulcerative Colitis, Uticaria, Interstitial Lung Disease and Asbestosis.
9/38 (24%) patients were diabetic, and 56% of them did not have intensification of their existing diabetic regime when required.
In the non-diabetic population, only 3/29 (10.3%) had blood glucose monitoring.
Recommendations
Most steroid use is usually less than 5 days, but 22% is for greater than 6 months and 4.3% longer than 5 years. We already know that steroid increases post-prandial glucose levels. The fluctuation in blood glucose levels is associated with increased cardiovascular mortality. However, more research is still needed. From this, we feel that in-patients on steroid doses greater than physiological doses should have should have their blood glucose measured while in hospital. On discharge with steroids, they should be advised on symptoms of diabetes and seek advice/treatment early.

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P218

Type 1 or type 3c diabetes: a diagnostic dilemma

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A 71 year old gentleman presented with polydipsia, polyuria and nocturia for two weeks and weight loss of 10.5 Kg over the preceding two years. He had hypertension controlled with valsartan, hydrochlorthiazide, amlodipine and doxazosin. His average alcohol intake was 55 units per week. His brother had diabetes of uncertain aetiology. Examination was unremarkable apart from mild dehydration. His body mass index was 28 kg/m^2 and there were no clinical signs suggestive of insulin resistance or lipodystrophy. Investigations showed venous glucose of 43.9 mmol/L, plasma ketones of 1.0 mm, HbA1c of 116 mmol/mol (12.8%), normal pH and renal function. He was initially managed with intravenous fluids and variable rate insulin infusion with smooth transition towards basal bolus insulin regimen. Due to excess alcohol intake and weight loss, a CT abdomen was undertaken which showed features suggestive of chronic calcifying pancreatitis and no evidence of malignancy. A diagnosis of secondary diabetes due to chronic pancreatitis (type 3c diabetes) was made and the patient was counselled for alcohol intake. Islet cell antibodies were negative but anti-GAD antibody was strongly positive at 1961 u/ml (reference range 1–5), challenging the diagnosis of secondary diabetes.
Acute pancreatitis has been reported to increase anti-GAD antibody levels by damaging GAD65 antigen, leading to transient or permanent insulin dependent diabetes. In contrast, islet autoantibodies were negative in a study of patients with chronic pancreatitis, even in the presence of a diabetogenic HLA haplotype. This case is unusual as GAD antibody titres usually tend to be lower in autoimmune diabetes (less than 100 U/mL). We propose that pancreatitis led to elevation in anti-GAD antibody levels causing autoimmune damage to islet cells leading to insulinopaenia. This case highlights the importance of keeping a broad differential when assessing a patient with diabetes.

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P219

Comparison of laboratory-based and near-patient glucose monitoring in critically ill patients

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Frequent measurement of blood glucose among hospitalized patients including those in critically ill areas is routinely practiced. Evidence suggests that tight glycaemic control among hospitalized patients reduced complications such as sepsis and has been shown to reduce length of stay. Most commercially available devices have not been assessed in critically ill patients, furthermore point of care (POC) glucose testing among paediatric population has exhibited a discrepancy greater than 20 mg/dL (1 mmol/L). Recent regulatory agencies voiced concern on the validly of POC deceives use in critically ill patients and the lack of adequate data on its accuracy.

This study examined the use of POC glucose measurement using Precision PXP (Abbott Diagnostics) in the monitoring of glucose in critically ill patients. Patients in intensive care units (adult and paediatric), in cardiac care units and those presenting to the emergency department were included in the study. Concurrent POC glucose measurements from 182 patients from those units were compared with laboratory-based glucose values measured using the Hexokinase methods (Cobas, Roche Diagnostics). Sixty three Patients were considered critically ill with a total of 438 samples analysed from all study patients. Glucose values ranged from 25 mg/dL (1.4 mmol/L) to 594 mg/dL (33.0 mmol/L). Bias ranged from −95 to 36 mg/dL (−5.3 to 2.0 mmol/L). Among critically ill patients' glucose levels ranged from 50 mg/dL (2.8 mmol/L) to 190 mg/dL (10.6 mmol/L). Overall percentage bias was less than 6%. Clarke and Consensus diagram showed 98–100% of data within area A indicating no impact on clinical action. This study showed no significant impact when using the Abbott PXP glucose meter on critically ill patients as compared with a laboratory-based methodology.

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P220

The diabetologist as a medical columnist: a 7-year experience

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Background

The Medical columnist has not always been welcomed by the Medical Community.The Lancet, in its August 30, 1873 editorial had pointed out with regrets that a weekly periodical, the *English Mechanic and World of Science* had inaugurated a medical column edited by a member of the London medical establishment. The editorial had concluded that "we cannot but regard such conduct as an infraction of the etiquette of the profession, and hardly worthy of a Fellow of the College of Physicians and officer of a London hospital". What was squashed more than a century ago as being unacceptable is today understood and supported. Diabetes is a disease state in which education plays a highly significant role in prevention and management. The Nigerian media; both print and electronic has been awash over the last decade with half truths and outright falsehood about diabetes peddled by self-styled alternative medicine "Consultants".

Table 1 Grouping of questions asked via SMS.

Question group	Frequency	Percentage
Life expectancy with diabetes	72	1.8
Prevention of diabetes	74	1.9
Fears about insulin use	82	2.1
Foot complications	200	5.1
Paresthesia	250	6.4
Diabetes complications	256	6.5
Cure for diabetes	650	16.6
Erectile dysfunction/fertility	700	17.8
Worries about poor control	752	19.2
Efficacy of herbal remedies	882	22.5
Total	3926	100

Methods

A Column titled "Diabetes corner" ran from February 2009 to March 2016 in *The Sunday Sun*, Nigeria's widest circulating Newspaper. The column educated individuals with and without diabetes. Readers were given the opportunity of communicating with the authour via voice calls, short message services (SMS) or email.

Results

Three thousand, nine hundred and twenty six (3926) SMS messages were received.

Conclusion

Newspapers are a viable resource in educating the populace. Orthodox medical practitioners must pick up the gauntlet of diabetes education and begin to use the print media to counter the currentlt prevalent misinformation and superstitions about diabetes.

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P221

A rare case of diabetes, hypogonadism and arthritis

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We present a challenging case of a 51 years old men, diagnosed with diabetes as he presented to emergency department with osmotic symptoms and hyperglycaemia. He was started on insulin and referred to diabetes clinic.

On review, glycaemic control was sub-optimal (HbA1c 94 mmol/mol) and his insulin was changed from biphasic to basal-bolus regimen. His BMI was 21 kg/m^2 and no family history of diabetes was reported. The Anti GAD antibody was negative. He had some circulating insulin and C-peptide level, though less than expected for given blood glucose. He was noted to have a modest sustained rise in ALT.

A detailed exploration of history revealed chronic polyarthritis of unknown aetiology, loss of libido and erectile dysfunction. He had not fathered children. Further workup showed secondary hypogonadism with otherwise normal anterior pituitary hormones, splenomegaly, mildly coarse Liver and osteoporosis at lumbar spine. He had normal echocardiogram and MRI of pituitary. Serum Ferritin was raised at 3132 ug/l (Ref range 30–284 ug/l). Serum iron and iron saturation was 51.4 μmol/l (Ref 9–32 μmol/l) and 110% (Ref 20–50%) respectively.

A diagnosis of Hemochromatosis Type 1 was confirmed by presence of HFE gene mutation – C282Y Homozygous mutation, causing secondary diabetes, arthritis and hypogonadism.

Patient was started on venesection fortnightly and testosterone replacement. Following treatment, significant improvement in general well-being and sexual function was reported. His diabetes is well controlled.

Hereditary Haemochromatosis is autosomal recessive condition, with vast majority homozygous for the HFE C282Y gene mutation. In the general population, 1 in 200 people have this genotype, but only a fraction proceeds to develop clinically relevant disease. The serious complications of haemochromatosis include Diabetes, liver cirrhosis, arthritis, cardiomyopathy and hypogonadism. An early treatment, normally by venesection, preserves normal life expectancy.

Haemochromatosis should be considered in differential diagnosis of secondary diabetes in patients with relevant symptoms.

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P222

Screening for coeliac disease in type 1 DM – A retrospective observational study in Harrogate District Foundation Hospital

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Coeliac disease is more common in people who have Type 1 diabetes mellitus (DM) because of their autoimmune co-existence. Between 4 and 9% of people with Type 1 DM will also have coeliac disease. The updated NICE guideline (NG 20 coeliac screening) recommends that adult with Type 1 DM should be tested for coeliac disease at diagnosis and retested if any symptoms of coeliac disease develop.

Study method & Result
Newly diagnosed type 1 DM from January 2012 till January 2017 were included. Total number of patients was 36 in 5 years period. Five patients had a coeliac screening (tTG) done at the time of DM diagnosis (14%). 9/36 (25%) patients had the test done anytime during follow ups. One patient had coeliac status retested, unfortunately no clinical indication noted for the rescreening.
We did a similar audit 5 months later, after our DE departmental educational meeting. There was a significant improvement in our results. About 70 % of patient has had their coeliac screening tests done at the time of type 1 DM diagnosis. 2 /10 (20%) had a positive test result, referred to gastroenterology for tissue diagnosis.
Conclusion
For most people, Type 1DM is diagnosed before coeliac disease, although it can happen the other way around. Some people with Type 1 DM appear to have mild or no obvious symptoms of coeliac disease, but their intestinal mucosa will still be damaged when they eat gluten. When coeliac disease is diagnosed before diabetes, the symptoms of diabetes tend to be more severe and there is a higher likelihood of other autoimmune diseases. Recurrent hypoglycaemia can be a sign of coeliac disease in people with Type 1 diabetes. In adults with type 1 diabetes, NG17 recommends assessment of markers for coeliac disease for patiens with low BMI or unexplained weight loss.We conclude from our study that we need to improve coeliac screening for all newly diagnosed type 1 DM as per current NICE recommendation.

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P223

Frequency of nonalcoholic fatty liver diasease in patients with diabetes mellitus

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Background
Nonalcoholic fatty liver disease (NAFLD) is commonly associated with type 2 diabetes mellitus (DM) though its prevalence is not well studied. This was a prospective study of prevalence and risk factors of NAFLD in patients with type 2 diabetes. The aim of this study was to determine the frequency of NAFLD in patients with T2DM.
Subjects and Methods
A total of 200 patients with T2DM fulfilling the criteria were enrolled after taking informed consent in Fall 2016/Spring 2017. Thorough medical history and relevant physical examination was taken. Demographic data such as age, gender were noted. Ultrasound was done and then patients were classified as having NAFLD if they had evidence of steatosis with no causes for secondary hepatic fat accumulation such as significant alcohol consumption, use of steatogenic medication, or hereditary disorders.
Results
The mean age of patients was 52.40 years with standard deviation of 2.68 years with most of the patients in the age range 45–60 years. Majority of the patients in the study were female (62.0%). Mean duration of DM was 6.2 years with standard deviation of 2.58. Mean fasting plasma glucose was 145.5 ± 5.36 mg/dl. Frequency of NAFLD, as per operational definition was 55%. Stratification of data with respect to age, gender, duration of diabetes and treatment of diabetes show P value was >0.05 in all cases showing statistically insignificant difference between various subgroups.
Conclusion
Prevalence of NAFLD in our cohort of type 2 DM patients is high. It can occur in diabetic patients without any symptoms, signs or routine laboratory test abnormalities and thus needs to be screened.

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P224

UHCW audit on SGLT2 inhibitor (SGLT2-i) use

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Aim
After almost 2 centuries, SGLT2-i have made their comeback in human pharmacology through successful re-introduction in diabetes type 2 (T2D). Via restriction of renal glucose reabsorption, SGLT2-i have shown promising results. The aim of this audit was to ensure that current practice at UHCW NHS Trust is in line with the agreed national standards, whilst collecting clinical data from the use of SGLT2-i.
Methods
This retrospective audit compared the use of all licenced SGLT2-I at UHCW NHS Trust. Data from 75 patients who received SGLT2-i through hospital-issued prescriptions from Jan.2014–Oct.2016 was collected. Medical notes and electronic files were examined for demographics, glycaemic and non-glycaemic cardiovascular outcomes, side effects and possible prescribing errors.
Results
Dapagliflozin was most commonly used till the published EMPA-REG outcome study in 2015, after which empagliflozin took its place. As far as timing of prescription is concerned, their addition appears to be late in T2D, most probably due to their recent approval. Our data show higher efficacy of canagliflozin in HbA1c reduction and better trend in BMI control. Urinary tract infections and thrush were one-off events, only 1 patient developed a new foot ulcer, urinary albumin excretion was improved, lipids were unaffected, there was no evidence of bone density reduction and liver function was most often improved or unaffected. With regards to prescription errors, 2 of the prescriptions were unlicensed for T1DM and 5 of the patients did not have normal baseline eGFR. Moreover, 5 of the patients were not started at the recommended dose.
Conclusions
In our sample, canagliflozin induced better glycaemic control and the effects on renal preservation were promising. SGLT2-i were safe in use but regular monitoring of their multi-systematic effects is essential. Prescribing errors can be avoided through staff re-education so that good quality of care is maintained.

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P225

Peripheral neuropathy and associated factors among type 2 DM patients in FMC Abeokuta

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Introduction
Peripheral neuropathy is one of the common complications of diabetes and it may progress to the insensate foot at risk for ulceration. It may be evaluated for using several methods which include biothesiometry and the Michigan Neuropathy Screening Instrument. Assessment of Vibration Perception Thresholds is a validated method of screening for neuropathy while the MNSI is a two part validated screening tool for assessing peripheral neuropathy in an outpatient setting.
Aim
To determine the prevalence of peripheral neuropathy and associated factors among type 2 DM patients in FMC Abeokuta.
Settings and Design
A descriptive cross sectional study of 414 type 2 diabetics attending the outpatient clinic of FMC Abeokuta in South West Nigeria.
Methods
414 patients were recruited using systematic random sampling method. Demographic /clinical data were documented in a questionnaire. The meaning three vpts readings was taken and values >25 volts was regarded as abnormal. The MNSI made up of fifteen 'Yes or No' questions on foot sensations and a brief physical examination was used. Peripheral neuropathy was defined as $>/ 7$ positive responses on the first part and $>/ 2$ points on the examination part of the questionnaire.
Statistical Analysis
Data was analyzed to determine the prevalence of peripheral neuropathy and associated factors.
Results
Prevalence of peripheral neuropathy was 65.7% and associated factors were age >65 years and diabetes duration >10 years ($P<0.001$).
Conclusion
The prevalence of peripheral neuropathy among outpatient type 2 diabetics in FMC Abeokuta is high. Associated factors include increasing age and diabetes duration, therefore optimal metabolic control, frequent foot screening programs for early detection and patient education is crucial for prevention of foot ulcers.

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P226

Gender differences IN glycaemic target in patient with type 2 DM at the obafemi awolowo university teaching hospitals complex ile-ife South West Nigeria

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Background
Diabetes Mellitus (DM) is increasing in prevalence worldwide. Sex differences in glycaemia attainment may be relevant in the management of type 2 DM.
This study determined gender differences in glycaemic targets in patients with type 2 diabetes attending the Obafemi Awolowo University Teaching Hospital Complex (OAUTHC), Ile- Ife.
Method
This cross-sectional descriptive study involved four hundred (400) type 2 diabetes patients, males and females, who were consecutively recruited from the diabetes clinic of OAUTHC, Ile-Ife from May to December 2014. Relevant clinical information and physical examination data were obtained. Venous blood sample was collected for fasting plasma glucose (FPG), and two hours postprandial blood glucose (2HPP), HBA1c, total cholesterol, LDL-C, HDL-C and triglycerides. Glycaemic target were set using FPG $<$ 7.2 mmol/l, 2HP$P<10.0$ mmol/l, HBA1c $<$ 7%, blood pressure $<$130/80 mmHg, total cholesterol $<$ 200 mg/dl, triglycerides $<$ 150 mg/dl, LDL $<$100 mg/dl and HDL $>$40 mg/dl (1.1 mmol/l) in males and $>$50 mg/dl (1.3 mmol/l) in females.
Results
Of the 400 patients with type 2 DM, 190(47.5%) were males and 210 (52.5%) were female respectively. The mean age of the study population was 60.6 + 9.93 years and duration of DM was 7.81 + 5.76 years.
Women had higher prevalence of hypertension (83.3% versus 72.1%) than men $P<0.05$. Mean total cholesterol was significantly higher in women (4.45 mmol/l) than in men (4.08 mmol/l); $P=0.001$ and more men achieved LDL treatment goals than women (69.5% vs. 59.0%, $P<0.05$).
More women reached the target glycaemic goals of $<$10 mmol/l for 2HPP and HBA1c of $<$7.0% than men $P<0.05$.
Conclusions
Women with T2DM had a worse profile in terms of hypertension and lipid goals; and men achieved therapeutic goals less frequently than did women in terms of glycaemia.
Key words: Type 2 diabetes, gender, hypertension, cholesterol, glycaemic goals.
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P227

Assessing the knowledge of diabetes management within psychiatric crisis resolution teams

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Aims and hypothesis
The aim of this study is to determine the baseline knowledge of diabetes and its management within two Psychiatric Crisis Resolution Teams based at NELFT NHS Foundation Trust. We hypothesise that attendance to diabetes seminars will lead to better knowledge of the condition's management.
Background
A 2014 NHS survey found that 6% of people with mental health conditions also suffered from diabetes. Furthermore, antipsychotic and antidepressant medications have varying impacts on blood glucose levels, increasing the risk of poor outcomes in this cohort of patients. In order to provide optimum care, healthcare professionals within an emergency psychiatry team need to be aware of the basic management of diabetes.
Methods
An online survey was created using the SurveyMonkey software. It consisted of 8 multiple choice questions regarding diabetes and its management with each question testing a particular construct. Participants were asked to state their job role and level of proficiency managing diabetes patients on a scale of 1 to 10 (1=no ability and 10=full proficiency). Results will be analysed according to job role, before and after attendance to a diabetes seminar.
Results
We have currently analysed the responses of one of the two teams before the seminar. Their response rate was 63%. Correct answers per participant ranged from 3-7 out of 8 questions. Doctors (median=7) performed better than nurses (median=5), occupational therapist (median=4), and those who did not state their job role (median=4). 83% knew the common diagnostic symptoms, 94% correctly answered the construct measuring retinopathy screening knowledge, while 76% knew how to manage hypoglycaemia. In contrast, identification and initial management of impaired fasting glucose were poorly answered (24% and 12% respectively).
Conclusions
Overall, the baseline diabetes knowledge based on results collected so far is satisfactory; however there seems to be a weakness in managing high fasting glucose states. We expect participants to score significantly higher following attendance to diabetes seminars.
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P228

Predictors of hypoglycemia in patients with type 2 diabetes mellitus in South Western, Nigeria

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Introduction
Hypoglycaemia is a common and serious complication of diabetes treatment especially in patients who do not have knowledge of the condition and personal glucose metres. Patients with very good drug compliance are at greater risk of developing hypoglycaemia. Sometimes hypoglycaemia among patients on insulin therapy could be symptomatic or asymptomatic. The present study is aimed at measuring the determinants and predictors of hypoglycaemia among diabetes patients.
Methods
The study was carried out at the endocrinology, diabetes & metabolism unit of Ladoke Akintola University of Technology Teaching Hospital, Ogbomoso. Questionnaires were served to the patients after informed consent were gotten. The data were analyzed using SPSS (version 21.0). A total of 113 patients were recruited into the study.
Results
About 59.3% of the respondents were females and the mean age of the respondents was 60.94±11.95 years. The prevalent occupation of the respondents was trading (33.6%) and civil service (31.9%). The average FBS and diabetes duration were 9.05±3.48 mMol/L and 5.00±4.43 years respectively. Eighty-one (71.7%) have experienced hypoglycaemia. The percentage of participants who have experienced hypoglycaemia who know the following symptoms (sweatiness, shivering, hunger, weakness, palpitations, anxiety, confusion, visual disruption, light-headedness, convulsion, headache, inability to concentrate, aggression and loss of consciousness) are 74.1%, 76.5%, 72.8%, 69.1%, 58.0%, 39.5%, 43.2%, 50.6%, 46.9%, 37.0%, 49.4%, 40.7%, 34.6%, 56.8%.
Conclusion
Appropriate authorities should look into increasing awareness of the predictors of hypoglycaemia among the diabetes patients. Self-monitoring of blood glucose should also be encouraged among the patients so as to prevent the chronic effects of hypoglycaemia.
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P229

Antenatal gestational diabetes mellitus care – An audit on follow-up visits and antenatal attendance

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Introduction
Currently there is no published data nationally in the rate of lost appointments for Gestational Diabetes Mellitus (GDM) care during the antenatal period.

Objective
To determine the rate of did not attend appointments (DNAs) for patients with GDM during their antenatal period and the differences in attendance between GDM and obstetric follow-up visits and their associated factors.
Methods
A retrospective examination of all the newly diagnosed patients with GDM during 2016 was conducted.
Results
31.6% of GDM patients didn't attend for at least 1 visit during their antenatal period compared to 12% of obstetric visits (P-value <0.0001). They attended 3 visits in average during their pregnancy. There was a significant difference between the age of regular attendants and non-attendants (mean age 35 vs 30 respectively). Most Irish patients (72.8%) attended their appointments regularly compared to only 52% of non-Irish nationals. Age & nationality appeared to influence the DNA rate.

Table 1 Overall study findings.

Characteristics	Frequency
Total no.	117
Non-Irish	25 (21%)
Mean age (s.d.)	33.9 (5.77)
Antenatal GDM DNAs	61 visits
Antenatal Obstetric DNAs	31 visits

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P230

Burden of obesity and hypertension in Nigerians with type 2 diabetes mellitus seen in a tertiary health facility

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Background
Obesity is increasingly becoming prevalent among the general population and in patients with type 2 diabetes mellitus in particular. This unhealthy association contributes to increased morbidity and mortality from cardiovascular complications in diabetic patients.
Objectives
The aim of this study is to determine the prevalence of obesity among type 2 diabetes mellitus patients.
Materials and Method
This was a cross sectional descriptive study of Nigerians with Type 2 diabetes mellitus attending the outpatient clinic of Obafemi Awolowo University Teaching Hospital, Ile-Ife. Socio-demographic information, anthropometric indices (weight, height, waist circumference and hip circumference) and blood pressure measurements were taken. Body mass index (BMI) and waist-hip ratio (WHR) were calculated for each subject.
Results
One hundred and seventy eight type 2 diabetes mellitus patients participated in this study, 112 (62.9%) females and 66 (37.1%) males. The mean age of participants was 60.7 ± 11.1. Ninety eight (55.1%) were hypertensive. Their mean BMI was 26.6 ± 5.1 kg/m^2 (females 26.8 ± 5.4 kg/m^2, males 26.3 ± 4.6 kg/m^2, $P=0.573$), mean waist circumference was 95.1 ± 11.4 cm (females 95.6 ± 11.5 cm, males 94.3 ± 11.4 cm, $P=0.456$). Generalized obesity (BMI >30 kg/m^2) was present in 28.1%, abdominal obesity in 90.2% of the females and 54.5% of the males. BMI correlated positively with WC, $r=0.81$, $P<0.001$; and with WHR, $r=0.27$, $P=$
Conclusion
The magnitude of obesity particularly abdominal obesity in our cohort of diabetic patients is high and which may have health implications. Early recognition of abdominal adiposity with appropriate measures on lifestyle modification is therefore important to mitigate this trend.
Keywords: Obesity, type 2 diabetes mellitus, OAUTHC
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P231

Diabetes clinic assessment: lookingout for diabetics' kidneys and toes

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Introduction
According to guidelines, to predict early signs of micro-vascular complications in patients with diabetes, regular foot examination and perform regular investigations which include HbA1c, urea and electrolytes (U+Es), albumin-creatinine ratio (ACR) and lipid profile.
Methods
During February 2017, consecutive patient medical notes were collected from a weekly general diabetic clinic. Using the patient notes and clinical portal blood test results, it was noted whether patients had had an albumin-creatinine ratio, lipid profile or urea and electrolytes checked within the last year, a HbA1c result within the last 6 months and if a neurovascular foot examination had been recorded in the clinic notes (either examined in clinic or recorded as being done by their GP in the last year).
Results
The notes of 156 patients were analyzed. The number of females to males was 68:88, the age range 16 to 88 years of age and the mean age 50 years. An up-to-date HbA1c result was available for 97.3% of patients, with an average result of 73 mmol/mol. Within the last year, 82.1% of patients had a U+E result available, with 50.6% an ACR and 52.6% a lipid profile result checked. A foot examination was recorded as having been done within the last year in 41.7% of clinic entries.
Conclusion
The audit clearly highlighted the issues in our practice as compared with NICE guideline recommendations, especially with the feet examination and the ACR requesting. Therefore, cooperation between the primary and secondary care is essential in the annual diabetic assessment. And electronic record may be a future solution.

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P232

Lifestyle patterns and diabetes risk in second generation South Asians

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South Asians are six times more likely to get diabetes than Europeans. One of the main factors linked with this increased risk is lifestyle factors. Around the late 1950s, those who lived in South Asia had a diet rich in carbohydrates and sugar. However, this was balanced through their exercising habits, as many were hard working labourers who had to physically strain themselves through manual work, therefore burning off those calories appropriately. The lack of public transport or cars in rural areas meant that travelling was through walking or cycling, maintaining a healthy lifestyle. Unfortunately, the following generations who immigrated to the Western countries, while keeping up with the South Asian food items and diet, adopted the Western lifestyle associated with obesity. Lifestyle changes meant that people had access to unhealthy food more easily, and luxurious lives lead to a decrease in physical work. This project aims to identify to what extent second generation South Asians living in the UK have adopted the Western lifestyle and highlight the possible risk factors.
A questionnaire aimed at second generation South Asians was devised and uploaded on Facebook. A total of 42 responses were obtained. 73.8% of participants consider their diet to be both western and Asian and 66.7% consume rice more than twice per week. 26.2% consume fast food between 6–10 times per month. 50% stated that their level of exercise was walking only. The younger South Asian generation seems to be adhering to the South Asian diet and over a quarter also consumes a Western diet linked to obesity while carrying out low to moderate levels of exercise. This further exacerbates their genetic risk of diabetes. There is a need to provide more support and guidance to this specific group, educating and preventing diabetes from early lifestyle modifications.

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P233

The Diabetologist as a Medical Columnist: A 7-year experience

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Abstract withdrawn.

P234

Transdermal delivery of *Syzygium aromaticum*-derived oleanolic acid by dermal patches in streptozotocin-induced diabetic rats: effects on some selected metabolic parameters

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Medical plants believed to be safe and cost effective than synthetic hypoglycaemic agents play important roles in the management of diabetes mellitus in developing countries where resources are meagre. We have isolated triterpenes from *Syzygium aromaticum* as the bioactive compounds that possesses hypoglycaemic effects in experimental diabetes. However, the poor water solubility of triterpenes observed in oral administration has necessitated the evaluation of alternative methods of administration for effective diabetes management. Accordingly, the aim of this study was to investigate whether transdermal application of *Syzygium aromaticum*-derived oleanolic acid patch (P-OA) formulations sustain controlled release of oleanolic acid (OA) into the bloodstream of STZ-induced diabetic rats with concomitant alleviation of some of the complications associated with diabetes. Topically applied P-OA patches containing various OA doses (21, 42 and 84 mg/kg) prepared by dissolving pectin/OA in deionised water with subsequent solidification with $CaCl_2$ were evaluated for oral glucose tolerance responses in groups of STZ-induced diabetic rats. Short-term (5 weeks) effects were assessed in diabetic animals treated thrice daily with P-OA patches 8 hours apart. Animals treated with drug-free pectin and insulin (175 µg/kg, s.c.) acted as untreated and treated positive controls, respectively. Blood and tissue samples were collected for the measurement of selected metabolic parameters. Blood glucose concentrations were significantly reduced following transdermal P-OA treatment thus indicating that OA was transported across the skin. The treatment also restored the reduced glycogen concentrations in muscle and hepatic tissues of diabetic animals to near normalcy. However, there was no change in plasma insulin concentrations of STZ-induced diabetic rats following acute and short-term daily treatment with OA-containing dermal patches. The data indicate successful sustained controlled release of OA into the bloodstream of STZ-induced diabetic rats via P-OA hydrogel matrix patches with a concomitant reduction in plasma glucose concentrations and amelioration of some selected metabolic parameters.

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Neoplasia, Cancer and Late Effects

P241

Population remodeling in the acquisition of endocrine resistance in breast cancer

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The cell-cell interactions that occur within the breast tumor microenvironment are critical determinants of cancer cell fate. In the face of treatment, the theory of clonal evolution dominates current thinking. Thus, individual cells may acquire a mutation(s) that provides a selection advantage, *i.e.,* Darwinian selection acts at the single cell level. We studied the effect of antiestrogen treatment on the population remodeling of admixtures of sensitive (S) and resistant (R) human breast cancer cells. R cells were derived from S cells by selection against antiestrogens. We labeled S cells with GFP and R cells with mCherry, mixed the cells in different ratios, and treated with antiestrogen or vehicle. Unlike other resistance phenotypes, R cells do not out-compete S cells, nor do S cells restrain R cell growth. Rather, R cells protect S cells from treatment. Full communication of the resistance phenotype occurs at a 1:1 mixture of S:R; ~75% of the R phenotype transfer is evident at 10:1. These results reflect improved fitness conferred by population interactions, not clonal evolution. SILAC analysis of S and R cells (pure populations) implicate differential regulation of *E2 response-early*; *E2 response-late*; *glycolysis; fatty acid metabolism*; *mTORC1 signaling*; *peroxisome*; *UPR; oxidative phosphorylation* in S vs. R cells. Clustering of iTRAQ-TAT data from pure and admixed S:R populations shows that the 1:1 and 5:1 treated, and the 1:1 untreated admixtures, cluster with pure R cells. Untreated 5:1 admixed cells cluster with untreated S cells. Thus, R and S cells alter each other's molecular signatures. Studies using scratch labeling and small molecule inhibitors show that R cells communicate with S cells via both juxtacrine and paracrine interactions mediated by gap junctional intracellular communication and secreted micro-vesicles, respectively. The molecular features modified reflect our unifying hypothesis of signaling and cell function control in endocrine resistance.

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P242

Combination of JQ1, an inhibitor of epigenetic pathways, and everolimus for treatment of pancreatic and bronchial neuroendocrine tumours

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Current treatments, including surgery, medical therapy, radiotherapy, and radionuclide therapy for neuroendocrine tumours of the pancreas (PNETs) and bronchus (BNETs) are often unsatisfactory, leading to a 5-year survival of $<50\%$ and 5%, respectively. PNETs and BNETs frequently have mutations in chromatin-remodelling genes and the protein encoded by the multiple endocrine neoplasia type 1 (*MEN1*) gene, menin. Menin binds the histone methyltransferase MLL1 and together with the acetyl-lysine recognising bromo and extra terminal (BET) family proteins plays an important role in tumour development. We have previously demonstrated that the BET inhibitor JQ1 can significantly decrease proliferation, and increase apoptosis of BNET and PNET cells *in vitro*, and PNETs *in vivo*. JQ1 treatment, however, did not lead to 100% cell death, and we therefore investigated for such effects using JQ1 in combination with everolimus, an inhibitor of the mechanistic target of rapamycin (mTOR) pathway. Treatment of the metastatic PNET cell line BON-1, and the less aggressive typical bronchial carcinoid cell line, H727, by everolimus alone reduced proliferation by 30% ($P<0.005$), and 40% ($P<0.05$), respectively, whilst JQ1 alone reduced proliferation by 70% and 50% (both $P<0.0005$), respectively, when compared to control treated cells. Furthermore, JQ1, but not everolimus, significantly increased apoptosis of BON-1 and H727 cells (2.7- and 3.3-fold respectively, $P<0{,}0005$). Combined JQ1 and everolimus treatment of BON-1 and H727 cells reduced proliferation by 86% ($P<0.0005$), and 81% ($P<0.0005$), respectively, when compared to control treated cells; this was also significantly ($P<0.0005$) higher than cells treated with JQ1 only. Furthermore, combined JQ1 and everolimus treatment of BON-1 and H727 cells increased apoptosis by 2.6-fold and 4.7-fold (both $P<0.0005$), respectively, when compared, to cells treated with JQ1 only. In conclusion, our results demonstrate that combined treatment of JQ1 and everolimus may provide a potential therapeutic regime for PNETs and BNETs.

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P243

Analysis of the diagnosis, treatment and genetics of 175 cases of phaeochromocytoma and paraganglioma in two ENETS Centres of Excellence

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Background
Phaeochromocytomas (PCC) and paragangliomas (PGL) are tumours derived from neural crest cells within the adrenal medulla or extra-adrenal ganglia, respectively. Over 20 known genes are implicated in at least 30% of cases. Experience with these tumours in individual centres is limited due to their rarity.
Objective
To describe the demographics, genetics, treatment and progression-free survival (PFS) in patients with PCC and PGL in two London ENETS Centres of Excellence.
Methods
Retrospective audit of 175 PCC and PGL patients diagnosed between 2000 and 2017.
Results
73 PGL and 102 PCC were analysed (83 male, 92 female). Median age of diagnosis was 51 for PCC and 48 for PGL. Most PGL were head and neck (44%) and abdomen (42%), with other sites including pelvis (8%) and thorax (1%). Genetic analysis was performed in 46 PGL (18 normal, 1 SDHAF2, 18 SDHB, 1 SDHC, 7 SDHD, 1 VHL) and 60 PCC (38 normal, 1 SDHA, 5 SDHB, 1 SDHD, 7 RET, 3 NF1, 5 VHL).
The primary treatment modality for both PGL and PCC was surgery (76% and 95%, respectively). The other treatment modalities utilised were more varied for PGL (9% radiotherapy, 6% Peptide Receptor Radionuclide Therapy [PRRT], 5% embolization, 2% somatostatin analogue, and 2% chemotherapy) than for PCC (3% 131-I MIBG and 1% PRRT).
Progression was observed in 45% of PGL cases after treatment and 20% in PCC. In those who progressed, the median PFS in PGL was 31 months (interquartile range 41) and 15 months for PCC (interquartile range 58). Mutation carriage (PGL and PCC) and abdominal vs head and neck localisation of PGL were associated with a higher probability of progression.
Conclusions
Our database describes one of the largest series of patients with PCC and PGL in Europe. Progression is more likely in PGL vs PCC, although the interval to progression is longer for PGL.

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P244

Identifying linkages between EDCs in personal care products and breast cancer through data integration and gene network analysis

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Abstract withdrawn.

P245

Assessment of protective factors from the development of radiation induced hypopituitarism: A single centre study

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Pituitary irradiation is a known risk factor for the development of subsequent hormonal dysfunction. However, it has been noted that some patients do not appear to be affected after many years of follow up. The aim of this retrospective study was to identify protective factors from developing radiation induced hypopituitarism (RIH).
Methods
This is a single center study of patients attending the late effects of childhood cancer service in Oxford University Hospitals NHS Foundation Trust. All patients that received at least 18 Gy radiation dose to the pituitary for the treatment of non-pituitary disease as a child and who have been in remission for at least 5 years were included. Up to 26 years of follow up information was available. Out of the 60 patients studied, 20 patients have not yet been diagnosed with any pituitary hormonal deficiencies (mean time since initial therapy of 17.5 years). All patients had pituitary function and clinical assessment annually. We assessed whether sex, age at radiation, tumour type, radiation dose and fraction size were protective factors in this cohort of patients.
Results
A lower radiation dose is protective in the development of RIH (average 37.1 vs 43.9 Gy; $P=0.02$). However, sex (39% of males vs 22% of females unaffected; $P=0.18$), average number of fractions (26.5 vs 27.4; $P=0.33$), age at radiation (9.5 yrs vs 9.9 yrs; $P=0.33$) and type of tumour were not protective.
Discussion
This single center study with a long follow-up period has identified a lower radiation dose as a protective factor from RIH in a subset of patients treated for childhood cancers. The current literature demonstrates disparity of understanding and has not yet explored this phenomenon. As the population of survivors increase it is essential that further studies take place in order to understand the sequelae of events in these patients.

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P246

The course of the endocrine disease in POEMS syndrome

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Introduction
POEMS syndrome is a rare multisystem disorder characterised by polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma-proliferative disorder and skin changes among other features. We describe the course of the endocrine disease in the context of this paraneoplastic syndrome.
Methods
Of the 60 patients with POEMS care in hospital, data are available for 43 patients who attended the Joint POEMS Clinic from 06/1999 to 05/2017. All patients had endocrine screening at every appointment including pituitary, thyroid and bone metabolism. Median and interquartile range and mean $\pm$ SD are used for quantitative variables and percentage for qualitative variables.
Results
67% of the patients are male. Age at diagnosis is 50.3[38.2–63.3] years and the median follow-up is 4.5[1.9–7.8] years. At diagnosis, 52.5% of the patients presented with endocrinopathy and 47.6% had more than one endocrine disease. From those, 40% had thyroid disease, 27.5% hypogonadism, 5% type 2 diabetes and 4.9% Addison disease.
During surveillance 92.7% of patients developed endocrinopathy. 65.1% of patients had hyperprolactinaemia with a 1.9 ± 0.94 fold increase above the upper limit of the normal, which in 57.1% of the patients it was transient. 62.9% had hypothyroidism (32.6% clinical, 30.3% subclinical), transient in 38.58% of patients. 33.3% presented with high IGF-1 (1.3 ± 0.2 fold increase), and it normalised in 36.4%. Addison disease was diagnosed in 14% of patients with no recovery of the adrenal function. Type 2 diabetes developed in 16.3% of patients and 72.5% had hypogonadism (33.3% secondary, 66.6% primary). Gonadal function recovered in 3 patients. None of them had parathyroid dysfunction.
Conclusion
In our cohort, endocrinopathy in POEMS syndrome was found in 50% at diagnosis and in 90% during follow-up. The multidisciplinary team managing patients with POEMS syndrome should include an endocrinologist. Patients should be systematically assessed for endocrinopathy, which can result in clinically significant symptoms. The most common deficiencies were hypogonadism, and hypothyroidism, both of which were readily remedied with pharmacological intervention. Normalisation of the endocrinopathy was common so on-going treatment thereof should remain under review.

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P247

Check point inhibitor monoclonal antibody therapy – Are there effective markers for endocrine immune-related adverse events?

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Introduction
Whilst effective, targeted checkpoint inhibitor monoclonal antibodies are associated with immune-related adverse events including endocrinopathies. Increased licensed oncological indications for these agents raise the need for effective screening, monitoring and ongoing treatment of endocrinopathies. The aim of our study was to investigate potential predictive factors that may identify patients at risk of endocrinopathies.
Method
Retrospective audit of 160 patients receiving treatment in a single center with Ipilimumab, Pembrolizumab and Nivolumab individually or in combination.
Results
Thyroid dysfunction in 9.3% (15/160) and hypophysitis in 7.5% (12/160) were the commonest endocrine effects. There was no significant difference in the mean age of affected (59 y, 33–82) and unaffected (66 y, 30–83) patients nor in gender susceptibility (Men 82/129 unaffected to 17/31 affected, Women 49/129 unaffected to 14/31 affected, $P=0.99$).
Early symptoms of thyroid dysfunction (hyperthyroidism) and hypophysitis (headache or visual disturbance) were absent in the majority. There was no consistent change in prolactin or gonadotrophin level. MRI pituitary showed no characteristic changes. Posterior pituitary function remained unaffected. Thyroid antibodies were tested in eight out of fifteen with thyroid dysfunction and four were positive. Recrudescence of quiescent Graves' ophthalmopathy occurred in one patient and insulin deficiency characterised by ketoacidosis occurred in two patients with pre-existing type 2 diabetes mellitus. The time to development of endocrinopathy was 3–24 weeks with no obvious safe cut-off for exclusion. Pembrolizumab was predominantly associated with thyroid dysfunction (53%), whereas hypophysitis (41%) was more frequent with Ipilimumab.
Conclusion
Age, sex, and early symptomatology were not helpful markers in predicting risk for endocrinopathy. Although more frequent early in treatment, endocrine dysfunction could occur almost 6 months after initiating treatment. Type 2 diabetes and Graves' disease in remission significantly increases risk. Vigilant long-term monitoring is warranted in this cohort particularly in those with previous autoimmune conditions.

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P248

In-house method for the detection of miRNA 145 and 21 in plasma samples of breast cancer patients using SYBR green reverse transcription-qPCR

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Background
A major challenge in the management of breast cancer (BC) is the search for biomarkers that are sensitive and less invasive. miRNAs are reported to be tissue-specific, stable and aberrantly expressed in different tumours, hence their emerging role as potential biomarkers in BC management.
Objective
The study focused on developing an in-house method for the detection of mir-145 and mir-21 using SYBR Green RT-qPCR in plasma samples of BC patients attending the Radiotherapy clinic.
Methods
Total RNA was extracted using glycogen modified TRIzol reagent and spin column from plasma samples. Extracted RNA was analyzed by NanoDrop (ND) spectrophotometry and confirmed using denaturing urea polyacrylamide gel electrophoresis (PAGE). Stem-loop reverse transcription (SLRT) primers for mir-145 and mir-21 were used to make cDNA. Real-time PCR amplification analysis was carried out in the presence of forward and universal reverse primers specific for mir-145and mir-21 conjugated using SYBR Green chemistry.
Results
ND Spectrophotometric analyses and smears of the PAGE image indicate the workability of the miRNA extraction method. Real time amplification curves showed that the miR-145 amplification and fluorescence correlated to an appreciable degree with the amount of RNA: S1, P4 (2.9 ng/l) > S7, P2 (5.4 ng/l) > S6, P3 (8.8 ng/l) > S2, P1 (4.3 ng/l) > S5, P6 (4.3 ng/l) > S3, P7 (3.2 ng/l) > S4, P8 (1.7 ng/l).
Conclusion
The RT-qPCR results validated the in-house technique for miRNA detection and showed the speed and sensitivity of the SL and SYBR Green I assay.
Key words: Breast cancer, miRNA, mir-145, mir-21, urea PAGE, SYBR Green RT-qPCR

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P249

Multiple endocrine neoplasia type 1 (MEN1) phenocopy due to a P.Leu380Phe cell division cycle 23 (CDC73) mutation

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Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disorder characterised by the combined occurrence of parathyroid tumours, and neuroendocrine tumours (NETs) of the pituitary and pancreas. MEN1 is caused by mutations of the tumour suppressor gene *MEN1*, and *MEN1* germline mutations are found in >75% of MEN1 patients. The remaining 25% of patients may have mutations involving as yet unidentified genes, or may represent phenocopies with mutations in other genes, such as for cell cycle division 73 (*CDC73*), calcium sensing receptor (*CASR*) and cyclin dependent kinase inhibitor 1B (*CDKN1B*). Here, we report a heterozygous c.1138C>T (P.Leu380Phe) *CDC73* mutation in a patient with clinically diagnosed MEN1 on the basis of the combined occurrence of primary hyperparathyroidism, acromegaly, and a pancreatic NET, which showed immuno-staining for glucagon and chromogranin A, but not insulin. Informed consent for genetic testing was obtained from the patient. DNA sequence analysis, using leukocyte DNA, of the *MEN1* gene did not reveal any germline abnormalities, and investigations for germline mutations in 6 other genes (*CDC73*, *CDKN1A*, *CDKN1B*, *CDKN2B*, *CDKN2C* and aryl-hydrocarbon receptor-interacting protein (*AIP*)) implicated in the aetiology of parathyroid and pituitary tumours was undertaken. This revealed the presence of a heterozygous P.Leu380Phe missense mutation of *CDC73*, mutations of which are associated with the hyperparathyroidism-jaw tumour syndrome (HPT-JT), an autosomal dominant disorder characterised by occurrence of parathyroid tumours, ossifying fibromas of the jaw, renal tumours and uterine tumours. Our findings are consistent with a previous report of a *CDC73* mutation (c.1239delA) in association with MEN1 phenocopy in a patient with primary hyperparathyroidism and a prolactinoma. Thus, our results, which expanded the spectrum of tumours associated with *CDC73* mutations to include somatotrophinomas and pancreatic NETs, further demonstrate that *CDC73* mutations can result in a phenocopy of MEN1.

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P250

Immunotherapy and development of endocrine dysfunction: An audit of immune checkpoint inhibitors

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Introduction
Immune checkpoint inhibitors such as CTLA 4 inhibitors (Ipilimumab) and PD1 inhibitors (Nivolumab/ Pembrolizumab) are being increasingly used for treatment of malignant melanomas and other solid tumours. Despite clinical benefits, they have been known to cause certain Immune related adverse effects (IrAEs) which may be dermatological, gastrointestinal, endocrine, or other immune phenomenon.
The endocrine side effects with checkpoint inhibition include hypophysitis, thyroid and adrenal dysfunction. However, there are currently no established monitoring guidelines.

Audit
Our aim was to check the monitoring of endocrine dysfunction in all patients undergoing treatment, and possibly devise guidelines for monitoring these patients long term.
We retrospectively reviewed all patients who received immune check point inhibitors either as single agents or in combination from 2013 to 2017 using the following standards for analysis (these standards were devised after discussion with Endocrine and Oncology consultants)
1. Baseline cortisol and thyroid stimulating hormone (TSH) to be checked for all patients prior to treatment.
2. Checking TSH and cortisol every cycle / monthly from the point of initiation of treatment up to 3 months after completion for all patients.

Data sources included outpatient clinic letters, electronic prescriptions, biochemistry results and multidisciplinary team meeting summaries. Analysis of quantitative data was in percentages and proportions.
Results and Conclusion
17% of patients developed endocrine dysfunction and there was inconsistent monitoring of endocrine function. This supports the need for a monitoring protocol for all patients starting immunotherapy to assess for endocrine dysfunction, as they could be potentially life threatening.

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P251

Endocrinopathies are a frequent Consequence of Immune Checkpoint Inhibitor Therapy, with a Low Recovery Rate of both Thyroid and Pituitary Dysfunction

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Background
Immune checkpoint (CTLA-4, PD-1) inhibitors are increasingly used to treat cancers including advanced melanoma. Although endocrine immune related adverse events (IRAEs) are now well reported, the frequency and type of thyroid and pituitary dysfunction reported varies considerably, with hypophysitis after CTLA-4 inhibitors reported in 2–16%, and thyroid dysfunction after PD-1 inhibitors in 2–39%. In addition, recovery rates for endocrinopathies are not well documented.
Methods
Retrospective case note review of all cases of endocrine IRAEs identified at our institution since introduction of ICI therapy, in order to determine the type and recovery rate of endocrinopathy.
Results
Since 2015, 19 patients developed endocrine IRAEs. Mean age 63 years (SD+/−13 years), mean follow-up 17 months (SD+/−8 months). All patients were referred to endocrinology and were investigated for recovery routinely.
Patients ($n=5$) developed hypophysitis a mean of 3.2 months following Ipilimumab. All had ACTH, TSH, Gonadotropin and Growth hormone deficiency; 2/5 had low prolactin concentrations (not measured in 3). Despite being assessed for recovery at regular intervals, all hormone deficits persisted.
Patients ($n=10$) developed thyroid dysfunction a mean of 2.9 months following Pembrolizumab ($n=8$) or Nivolumab ($n=2$). Primary hypothyroidism occurred in 6/10 cases. One case each of hyperthyroidism, thyroiditis and subclinical hyperthyroidism were identified. Secondary hypothyroidism occurred in 1 case and may not have been treatment related. The majority ($n=8$) remain on treatment.
Patients ($n=4$) treated with combination therapy developed thyroid dysfunction ($n=3$); 2 primary hypothyroidism and 1 thyroiditis; and hypophysitis ($n=1$).
Conclusions
Panhypophysitis occurred in all patients who developed pituitary disease; none recovered. Primary hypothyroidism was the commonest form of thyroid dysfunction. Despite interval surveillance for endocrine recovery, resolution was infrequent, suggesting that this form of IRAE (in contrast to others) is permanent. Such information is valuable when counselling patients of the risks and benefits of ICI treatment.

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P252

Primary pulmonary typical carcinoid as a source of ectopic Adrenocorticotropic hormone (ACTH)-dependant Cushing's

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Ectopic ACTH is rare and represents about 10% of causes of Cushing's syndrome. Associated tumours are neuroendocrine in origin and include small cell lung cancer, carcinoid tumours, and medullary carcinoma of the thyroid. In this report, we describe a rare case of ectopic ACTH due to a primary pulmonary carcinoid tumour.
A 29 years old male was diagnosed with hypertension 18 months prior to presentation. On examination, he had dark striae on his abdomen and axilla, and complained of muscle wasting, myalgia, fatigue, and facial acne. Suspected Cushing's syndrome was confirmed biochemically with random cortisol at 980 nmol/L (35.5 mcg/dL) and ACTH at 159 pg/mL (35 pmol/L). Following 8 mg dexamethasone suppression, a 24 hour urine free cortisol of 59 mcg (162 nmol) confirmed the clinical findings. Radiological investigation showed normal adrenal glands and pituitary imaging showed slight enhancement but could not exclude a micro-adenoma. Inferior petrosal sinus sampling (IPSS) for ACTH was performed.
Laboratory findings: Hyperglycaemia on presentation with HbA1c at 9.6%, moderate hypernatremia (151 mmol/L), normal renal function, persistent hypokalaemia <3.6 for two years with normal bicarbonate levels except for two occasions of mild alkalosis (bicarbonate 33 mmol/L). IPSS ACTH levels showed flat response in both petrosal samples (ratios to venous levels <2) and was diagnostic of ectopic ACTH production. Chest CT showed a 2.4 cm upper lobe lesion which was suspected to be an intrapulmonary bronchogenic cyst. An octreotide scan showed the lesion to be Octreotide avid. A right upper lobectomy and mediastinal lymph node dissection was subsequently performed and histology showed a unifocal typical carcinoid tumour measuring $2.1\times1.8\times1.6$ cm, with 2/3 lymph nodes positive for metastatic tumour. Immunohistochemistry was positive for ACTH. On follow up the patient was doing well. His Cushing's resolved and he showed sustained weight loss, control of this diabetes improved (HbA1c 6.0%), and his hypertension was controlled with amlopidine (5 mg).

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P253

Challenges in diagnosis and management of tumour induced oncogenic osteomalacia

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The combination of hypophosphataemia and hypercalcaemia has numerous aetiologies, which can be challenging in the clinical setting. Careful early biochemical identification will facilitate appropriate further imaging and management. We report a case of a gentleman who presented in his ninth decade with deteriorating cognition, proximal muscle weakness and reduced mobility on a background of hypertension, type 2 diabetes with associated retinopathy and stage 3 Chronic Kidney Disease (CKD). On admission biochemistry revealed hypophosphataemia (0.70 mmol/L), hypercalcaemia (3.42 mmol/L), an elevated serum alkaline phosphatase but a suppressed serum parathyroid hormone (PTH) with a low vitamin D level (47.7). The overall picture was consistent with non

PTH mediated hypercalcemia secondary to oncogenic osteomalacia. No elevation in tumour markers including prostate specific antigen, alpha feto protein and serum beta-hCG was observed. In order to delineate underlying aetiology it was agreed for him to undergo CT of chest, abdomen and pelvis which revealed evidence of disseminated intra thoracic and abdominal malignancy and a primary gastric malignancy which was evident as linitis plastica. His initial hypercalcemia was managed conservatively and hypophosphatemia reversed with intravenous incrementation. It led to objective improvement in his cognition and mobility. Oncogenic ostemalacia is a challenging diagnosis and overall aetiology is mediated by fibroblast growth factor 23 (FGF23) leading to tubular phosphate wasting and impaired Vitamin D hydroxylation associated with low 1α-hydroxylase activity. This case highlights importance of timely recognition of this difficult pathology. We advocate the use of early imaging in to facilitate early recognition of underlying tumour load and timely treatment. There might be a role for FGF 23 measurement in clinic setting to aid advance decision making.

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P254

Giant insulinoma: an unusual cause of hypoglycaemia

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Abstract withdrawn.

P256

Endocrine adverse effects after immune checkpoint inhibitor therapy in patients with metastatic melanoma: Experience from a single tertiary level centre

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Abstract withdrawn.

Neuroendocrinology and Pituitary

P261

Morbidity and mortality in patients with hyperprolactinaemia: The prolactin epidemiology, audit, and research study (PROLEARS)

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Purpose
High serum prolactin concentrations have been associated with adverse health outcomes in some but not all studies. This study aimed to examine the morbidity and all-cause mortality associated with hyperprolactinaemia.
Methods
A population-based matched cohort study in Tayside (Scotland, UK) from 1988 to 2014. Record-linkage technology (biochemistry, prescribing, hospital admissions, cancer registration, maternity data, mortality and demography) was used to identify patients with hyperprolactinaemia and were compared to an age-sex matched cohort of patients free of hyperprolactinaemia. The number of deaths and incident admissions with diabetes mellitus, cardiovascular disease, cancer, breast cancer, bone fractures, and infectious conditions were compared by means of survival analysis.
Results
We identified 1,204 patients with hyperprolactinaemia (exposed group) and 5,888 age and sex matched unexposed patients as a comparison cohort. The majority of patients were women (78%) with a mean age of 39 years, and the total follow-up was 70,836 person-years with a mean follow-up of 10.1 years (SD 6.9). Patients with prolactin-secreting pituitary tumours had no increased risk of diabetes, cardiovascular disease, bone fractures, all-cause cancer or breast cancer. Whilst no increased mortality was observed in patients with pituitary microadenomas (HR = 1.65, 95%CI: 0.79–3.45), those with macroadenomas demonstrated increased death risk (HR = 2.81, 95%CI: 1.42–5.58), although this was not correlated with the degree of serum prolactin elevation. Increased mortality risks were also observed in those with drug-induced hyperprolactinaemia, together with increased frequency of diabetes and cardiovascular disease, but again this was not directly associated with serum prolactin concentration. None of the groups demonstrated increased rates of cancer (HR = 0.98, 95%CI: 0.56–1.71).
Conclusions
No increased morbidity was observed in patients with prolactin-secreting pituitary tumours, whilst the increased mortality associated with pituitary macroadenomas was not correlated to the degree of serum prolactin elevation. Raised serum prolactin concentrations are unlikely to be directly related to adverse health outcomes.

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P262

Establishing the prevalence of pituitary involvement in patients with IgG4-related disease.

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Background
IgG4-related disease is a rare immune-mediated inflammatory condition associated with extensive multi-organ involvement. Little is known about the epidemiology of pituitary involvement as a part the IgG4-related disease spectrum.
Objectives
We aimed to identify patients with pituitary involvement amongst those with systemic IgG4-related disease, and to compare these individuals to patients with isolated IgG4-related hypophysitis. We also aimed to analyse the utility of serum IgG4 levels in assessing the degree of organ involvement.
Methods
A database was created using pre-existing patient data obtained from electronic patient records. Patients who satisfied the inclusion criteria were systematically screened for anterior and posterior pituitary dysfunction. Screening involved a short hypophysitis symptom screening interview followed by biochemical testing.
Results
A total of 13 patients with systemic IgG4-related disease were successfully screened. An additional 3 patients with isolated IgG4-related hypophysitis were identified. In the group with systemic disease, the female:male ratio was 1.6:1 and the mean age was 59.8 years $\pm$ 12.0 in this cohort. One male was identified to have pituitary involvement, equating to a prevalence of 8%. This patient differed by sex, ethnicity, age, clinical presentation and hormonal profile to those with isolated IgG4-related hypophysitis. We also found a positive trend between serum IgG4 levels and number of organs involved in the disease, although this was not significant.

Conclusion
We conclude that pituitary involvement is a rare but noteworthy clinical manifestation of IgG4-related disease. Biochemical pituitary screening is not justified in all patients with IgG4-related disease, and should only be considered in patients presenting with symptoms of anterior or posterior pituitary dysfunction. We also postulate that isolated IgG4-related hypophysitis may be a distinct clinical entity from systemic IgG4-related disease with pituitary involvement.
Keywords: IgG4, IgG4-related disease, Hypophysitis, Pituitary, Prevalence, Screening
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P263

Kisspeptin in the posterodorsal medial amygdala modulates sexual partner preference and anxiety in male mice

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The posterodorsal medial amygdala (MePD) is a neural site in the limbic brain involved in regulating emotional and sexual behaviours. There is however limited information on the specific neuronal cell type in the MePD functionally mediating these behaviours in rodents. The recent discovery of a significant kisspeptin neurone population in the MePD has raised interest in the possible role of kisspeptin and its cognate receptor in sexual behaviour. This study therefore tested the hypothesis that the MePD kisspeptin neurone population is involved in regulating attraction towards opposite sex conspecifics, sexual behaviour, social interaction and anxiety response by selectively stimulating these neurones using the novel pharmacosynthetic DREADDs (designer receptors exclusively activated by designer drugs) technique. Adult male Kiss-Cre mice received bilateral stereotaxic injections of a stimulatory DREADD viral construct (AAV-hSyn-DIO-hM_3D(Gq)-mCherry) targeted to the MePD which were activated by intraperitoneal (i.P.) injection of clozapine-N-oxide (CNO). Socio-sexual behaviours were assessed in a counter-balanced fashion after i.P. injection of either saline or CNO (5 mg/kg). Selective activation of MePD kisspeptin neurones by CNO significantly increased the time spent by male mice in investigating an oestrous female as well as duration of social interaction. Additionally, after CNO injection the mice appeared less anxious; evidenced by longer exploratory time in the open arms of the elevated plus maze. However, levels of copulatory behaviour were comparable between CNO and saline treated controls. These data indicate that DREADD-induced activation of MePD kisspeptin neurones enhances sexual partner preference in males and social interaction and decreases anxiety, suggesting a key role played by MePD kisspeptin in sexual motivation and social behaviour.
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P264

Early post-operative morning serum cortisol measurement as a predictor of remission of Cushing's disease

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Background
Determining post-operative remission in Cushing's disease is challenging. There is no consensus for the post-operative serum cortisol value which reliably predicts remission of Cushing's disease following trans-sphenoidal surgery. Traditionally, an early post-operative serum cortisol of below 50 nmol/L has been used to predict remission, but achieving this is often at the expense of hypopituitarism.
Objective
To identify whether post-operative day five 9AM serum cortisol is an accurate predictor of remission following trans-sphenoidal surgery for Cushing's disease.
Methods
Post-operative day five 9AM serum cortisol data were retrospectively reviewed for 39 trans-sphenoidal surgeries for Cushing's disease (January 2006 to April 2017). The day of trans-sphenoidal surgery was designated post-operative day one. Post-operative glucocorticoid replacement was omitted for 18–24 hours prior to sampling. Remission was defined as an absence of clinical or biochemical evidence of hypercortisolism for at least six months and up to five years post-operatively.
Results
The remission rate was 69.2% (27/39). Area under the receiver operating characteristic curve for post-operative day five 9AM serum cortisol as a predictor of remission of Cushing's disease following trans-sphenoidal surgery was 0.98 (95% CI 0.94 – 1.02). A cut-off of 195 nmol/L provided the highest sensitivity (100%) and specificity (92.6%) with a positive predictive value (PPV) of 85.7% and negative predictive value (NPV) of 100%. In contrast, using the traditional cut-off of 50 nmol/L produced 100% sensitivity, 51.9% specificity, 48% PPV and 100% NPV.
Conclusions
Post-operative day five 9AM serum cortisol is a reliable predictor of remission of Cushing's disease. A cut-off of 195 nmol/L for serum cortisol yielded the greatest diagnostic accuracy of remission of Cushing's disease for up to five years following trans-sphenoidal surgery. The traditional cut-off of less than 50 nmol/L was less reliable at predicting remission.
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P265

Is ^{11}C-methionine PET co-registered with MRI a game changer for persistent acromegaly?

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Aims
^{11}C-methionine positron emission tomography co-registered with MRI (met-PET/MRI) is a new imaging technique used for functioning pituitary adenomas. In patients with persistent acromegaly after primary therapy, met-PET/MRI can help identify the site(s) of residual pituitary adenoma when MRI appearances are inconclusive and direct further targeted intervention (Trans-sphenoidal surgery-TSS or radiotherapy).
Methods
Retrospective study of patients with acromegaly under active follow-up in a teaching hospital. Data were collected from paper and electronic records (2009 onwards). An arbitrary age cut-off of 75 was used when considering suitability for repeat TSS. Remaining patients were divided into three categories. P1: poorly controlled on somatostatin analogue (SSA) therapy and/or pegvisomant. P2: well controlled on SSA. P3: poorly controlled on dopamine agonist (DA) therapy
Results
Fifty-one patients were included, 61% female. Mean age 58.9 ± 16.5 years. Mean age at diagnosis 43.4 ± 16.9 years. Median follow-up of 13 years, IQR: 15.5. Twenty-three patients under the age of 75 were receiving ongoing medical treatment (P1: 10, P2:8 and P3:3). Annual cost (BNF 2017) of medical endocrine therapy for P1 category patients was £150,829 and P2 category patients was £73,466. Eight P1 category patients, willing for further intervention, have agreed to met-PET/MRI. Illustrative case: A young female patient with acromegaly on SSA + DA (P1) and diabetes mellitus on 120 units of insulin/day, both poorly controlled, underwent redo TSS influenced by met-PET/MRI (fused images). She was discharged off insulin and with intact steroid axis.
Conclusion
So far, our patients who have undergone met-PET/MRI have shown identifiable residual functioning pituitary adenoma. It has influenced our decision to put these

patients forward for TSS. There are potential cost savings involved if they are able to come off medical therapies or even decrease frequency of these injections.
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Patterns of recurrence, response to treatment and mortality in patients with malignant phaeochromocytomas and paragangliomas. – a single centre experience

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Introduction
Histology is a poor predictor of the malignant potential of phaeochromocytomas and paragangliomas (PPGL) and only the presence of distant metastasis confirms malignancy. This study reviews patterns of recurrence, treatment and mortality in patients with malignant PPGL presenting to our department at UCLH over 30 years.
Materials and Methods
In our series of 128 patients with PPGL, 26 (20%) with malignant tumours [male = 14, mean age 43 years (5–71)]; eight had synchronous (5 paragangliomas, 3 phaeochromocytomas) and 18 metachronous metastases (10 paragangliomas, 8 phaeochromocytomas). There was no correlation between histology and the potential for malignant disease. The mean duration between operation and the diagnosis of metastatic disease was 38 months (22–228) for paragangliomas and 78 months (11–299) for phaeochromocytomas. The sites of metastases in paragangliomas were bone (9), liver (6), lung(4) and in phaeochromocytomas; liver(7), lung(6) and bone(4). Local recurrence/persistence disease was associated with distant metastasis in 18 (70%) patients.
I123-MIBG scans were avid in 6/15(40%) paragangliomas and 10/11(91%) phaeochromocytomas. Twenty-two patients received radio-targeted treatment with 131I-MIBG and/or 90Y-DOTA-octreotate/LuDO. 131I-MIBG treatment stabilized disease in 2/7(29%) paragangliomas and 7/8(87%) phaeochromocytomas. 90Y-DOTA-octreotate was associated with a much better response rate in paragangliomas, with stabilisation in 7/9 (78%) patients.
External beam radiotherapy was used in four (18%) patients who had aggressive disease with bone metastases. During the mean follow-up of 80 months (5-300), 7 patients (27%) died of recurrent disease (5 paraganglioma, 2 phaeochromocytoma).
Discussion and Conclusion
In our series 20% of patients with PPGL had malignant disease with recurrence developing earlier in patients with paragangliomas. The patterns of metastases were similar for both paraganglioma and phaeochromocytoma. One third of patients with malignant PPGL died of their disease. Strict long term follow-up is recommended for all patients with PPGL for early detection of disease recurrence.
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^{11}C-methionine PET can aid localisation of the source of ACTH-dependent Cushing's syndrome in patients with equivocal or negative conventional imaging.

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Background
Cross-sectional imaging (e.g. CT/MRI) can not always reliably identify the site of ACTH secretion in Cushing's disease (CD) or the ectopic ACTH syndrome (EAS). We report our experience of localising the source of ACTH-dependent Cushing's syndrome, using functional imaging with ^{11}C-methionine positron emission tomography (Met-PET).
Methods
Forty consecutive patients with: (i) de novo Cushing's disease ($n=18$), (ii) residual or recurrent Cushing's disease following previous pituitary surgery and/or radiotherapy ($n=15$) or (iii) ectopic Cushing's syndrome ($n=7$) were imaged between 2011 and 2017. Patients underwent Met-PET and 3D gradient echo MRI of the sella. Co-registration of PET–CT with MR images was performed to yield Met-PET/MRI. Detailed mapping of ^{11}C -methionine uptake across the sella in three planes (coronal, sagittal and axial) was performed to allow correlation of functional data obtained from Met-PET with structural/anatomical data obtained from MRI. For those with EAS, additional Met-PET/CT studies of the neck, thorax and upper abdomen were performed.
Results
Eleven patients (60%) with de novo Cushing's disease and 10 patients (67%) with recurrent/residual Cushing's disease, but equivocal or negative cross-sectional imaging, had tumour successfully localized using Met-PET/MRI. In four patients (57%) with EAS, Met-PET/CT revealed sites of primary or metastatic disease, including in one patient with repeatedly negative cross-sectional imaging. Of the three remaining patients with EAS but negative Met-PET/CT, two also had negative cross-sectional and other functional (^{18}F-FDG and/or ^{68}Ga-PET-CT) imaging studies; in one patient, ^{68}Ga-PET-CT identified a small pancreatic primary tumour.
Conclusions
We report findings in the largest cohort of patients with ACTH-dependent Cushing's syndrome who have undergone functional imaging with Met-PET. Although this technique does not localize the site of ACTH-secretion in all cases, it is a useful adjunctive imaging modality for patients with negative/inconclusive findings from conventional imaging studies, especially in those with persistent/recurrent disease.
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Disorganised anterior pituitary ultrastructure in choriogonadotrophin-alpha (*Cga*) null female mice

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Choriogonadotrophin-alpha (*Cga)* is one of the first molecular markers for the developing pituitary gland previously known as 'alpha-subunit', common to thyroid-stimulating hormone (TSH), luteinising hormone (LH) and follicle-stimulating hormone (FSH). Mice lacking *Cga* are hypogonadal and exhibit profound hypothyroidism and dwarfism. Light microscopy of *Cga* null mice has shown that pituitary thyrotrophs in the absence of thyroid function display dramatic hypertrophy, somatotrophs were reduced in number and lactotrophs absent, whereas gonadotrophs were unaffected (Kendall et al 1995 Genes Dev 9:2007). The aim of the present study was to compare pituitary ultrastructure in *Cga* null and control WT mice. Pituitary glands (8 week old) were collected ($n=4$) and prepared for quantitative electron microscopy. Immunogold labelling of pituitary cell markers was performed to identify cells. Thyrotrophs in *Cga* null mice have more than twice the diameter of WT cells. The cisternae of the endoplasmic reticulum (ER) in WT cells appeared normally thin and elongated, comprising only a small portion of the cytoplasm. In *Cga* null thyrotrophs and gonadotrophs virtually the entire cytoplasm was filled with dilated ER cisternae. Scarce secretory granules were observed in mutant thyrotrophs and gonadotrophs, probably because heterodimerization of CGA and beta subunit is required. The christae of mitochondria in thyrotrophs in Cga null mice were markedly more electron dense than in control WT mice, and were in close contact with the ER. This mitochondrial phenotype is similar to that reported following exposure to oxidative stress. Somatotroph secretory granules were significantly smaller, fewer in number and distributed to the perimeter of the cell indicating increased GH secretion to compensate for reduced somatotroph number. These findings suggest disrupted pituitary cell function in the cellular compartments responsible for energy production and protein synthesis, folding, assembly and secretion.
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Male IGSF1 deficient humans and mice exhibit somatotroph neurosecretory hyperfunction

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X-linked *IGSF1* (immunoglobulin superfamily, member 1) loss-of-function mutations in males are associated with central hypothyroidism, macroorchidism, and a variable spectrum of anterior pituitary dysfunction. *Igsf1* deficient male mice also exhibit central hypothyroidism, however, the physiological and molecular function of IGSF1 in both species has not yet been elucidated. Although partial transient GH deficiency is a rare association of childhood *IGSF1* deficiency, affected adults exhibit IGF-1 levels above the mean and are anecdotally reported to have acromegaloid features consistent with mild GH excess. We therefore evaluated the role of IGSF1 in human and murine somatotroph function, which is currently poorly-defined.

IGSF1 deficient adult men demonstrated acromegaloid facial features (52% *vs.* 19% controls $P=0.024$) and increased head circumference, HC (>2 SDS in 30% cases). Median basal (3.51 *vs.* 1.05 μg/L/24 h), pulsatile (34.18 *vs.* 18.99 μg/L/24 h,) and total GH secretion (36.00 *vs.* 20.83 μg/L/24 h) were elevated compared with controls ($P\leq0.01$) and IGF-1 SDS was significantly elevated (1.0 ± 1.4 SDS vs. -0.4 ± 0.8 in controls $P=0.043$). HC was positively correlated with both pulsatile ($r=0.911$, $P=0.011$) and total GH secretion ($r=0.893$, $P=0.017$).

In comparison with wild type littermates, male $Igsf1\Delta^{exon1}$ null mice demonstrated features of GH excess including comparative increases in mean lean mass (13%, $P=<0.01$) and skeletal dimensions (eg femoral length; 3.7%, $P<0.001$). Serum IGF-1 was elevated in 10 week-old knockout mice (mean 431 ± 32 vs. 334 ± 26 ng/ml, $P=0.02$) and correlated with final body weight ($r=0.54$, $P=0.02$). Although no difference in GH secretion was observed, assessment of a more recently generated knockout line ($Igsf1\Delta^{312}$) demonstrated enhanced pituitary *Gh* mRNA expression.

We delineate a somatotroph neurosecretory hyperfunction associated with IGSF1 deficiency in humans and mice. These observations substantiate a hitherto uncharacterized role for IGSF1 in somatotrophs and suggest that evaluation of patients with *IGSF1* mutations for long-term consequences of increased GH exposure may be indicated.

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Smoke-induced nausea; mediated by the release of the lung tachykinin, endokinin, into the circulation?

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Nausea/vomiting induced by smoke inhalation is a common phenomenon, possibly explaining why many people who have a naturally strong reaction rarely take up smoking tobacco. The tachykinins are an ancient family of bioactive peptides distinguished by the common C-terminal motif, Phe-X-Gly-Leu-Met-amide. In humans, there are four members: substance P (SP), endokinin (EK) also known as hemokinin (HK), neurokinin A and neurokinin B, which signal through three G protein-coupled neurokinin receptors (NK1-3Rs). Whilst the expression of SP is limited to neural tissue, the EK gene is expressed in lung and placental tumour cell-lines and in many peripheral tissues, including placenta and lung, where EK/HK immunoreactivity has also been detected. As only SP and EK/HK signal strongly through the NK1R, and stimulation of these receptors in the area postrema by peripheral injection of SP induces vomiting in ferrets, placental EK has been proposed as the NK1R agonist that causes morning sickness (*The Endocrinologist* 115 p26). The nausea and vomiting experienced by patients undergoing cisplatin therapy is alleviated by NK1R antagonists. Using affinity purified antibodies raised against EK (12–30) and EK (32–41) in a two-site immunometric assay to measure EK-41 in Sepak-extracted plasma, it was found that the blood level of EK-41 in five non-smokers was 11–18 pg/ml. In a smoker who hadn't inhaled smoke for two hours, plasma EK-41 was 21 pg/ml; 10 min after smoking, it had increased nearly two-fold to 41 pg/ml, falling to 16 pg/ml two hours later. A non-smoker's plasma concentration of EK41 was 16 pg/ml but increased 29-fold to 466 pg/ml 10 min after inhalation of smoke; nausea was experienced two hours later, with levels of EK-41 then at 155 pg/ml. Together, these observations suggest that the lower incidence of nausea/vomiting experienced in both pregnancy and cisplatin therapy in individuals who smoke tobacco may result from downregulation of area postrema NK1Rs by circulating lung endokinin.

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P271

Inpatient prescribed desmopressin nasal spray is omitted three times more often than desmopressin prescribed by other routes

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Over the past decade there has been increased recognition of the dangers associated with inpatient management of diabetes insipidus (DI) and omission of desmopressin. An NHS England patient safety alert was issued in 2016 highlighting this risk.

Method

Using electronic prescribing records we reviewed all desmopressin prescriptions and omissions over a 12 month period in a large teaching hospital.

Results

Ninety-seven inpatients were prescribed 1367 doses of desmopressin during the year. The mean number of doses per patient was 14, with a range 1–388 doses and a median of 2 doses.

In 69% of patients (67/97) the indication was DI. Thirty patients received desmopressin for a range of other indications including haemophilia, suspected platelet dysfunction, and urinary continence problems. 77% of all doses were prescribed on neurology and neurosurgical wards.

Overall 5% of prescribed desmopressin doses were omitted (66/1367). The rate of omission was 18% for desmopressin nasal spray and 4–5% for oral or injected desmopressin (Table 1).

Discussion

Desmopressin omissions occur for both legitimate reasons (e.g. hyponatraemia) and inappropriate reasons (including lack of drug availability). This study shows that the intranasal formulation is especially likely to be omitted. The reason for this is the subject of future work, but we speculate that nasal medications (along with inhalers and eye drops) may be perceived by staff as less clinically important than oral or injectable medications.

Table 1 Frequency of observed desmopressin dose omissions by route.

	Prescribed doses	Doses omitted	Omission rate %
Injection	339	12	4
Nasal	56	10	18
Oral	972	44	5
Total	1367	66	5

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The severity of obstructive sleep apnoea does not influence ambient IGF-I levels

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Introduction
Obstructive sleep apnoea (OSA) is reported to have effects on a number of hormone systems including glycaemic control, catecholamines, and the HPA axis. In this study we aimed to determine the impact of OSA on IGF-I levels.
Patients & Methods
This is a prospective cohort study performed at Leeds Teaching Hospitals. Patients were recruited from the Sleep Apnoea Clinic between November 2014 and May 2017, following diagnosis of OSA. Serum samples were taken for measurement of IGF-I, and data collected on BMI, apnoea-hypoapnoea index (AHI) as a severity of OSA.
Results
448 participants were recruited (68% male, 32% female) with a mean age of 53.3 ± 12.6 years and a mean BMI of 36.0 ± 7.8 kg/m^2. T2DM was present in 77(17.2%), and pre-diabetes in 25(5.6%). The severity of OSA as assessed at the time of the study was as follows: 9 patients (2%) without current evidence of OSA; 122 (17.2%) with mild OSA; 117 (26.1%) with moderate OSA and 200 (44.7%) with severe OSA.
A positive correlation was demonstrated between OSA severity and both BMI $r=0.177$ ($P=0.0005$) and age; $r=0.106$ ($P=0.0245$), and a negative correlation between OSA severity and female gender; $r=-0.155$ ($P<0.001$). Although IGF-I levels were dependent on BMI; $r=-0.153$ ($P=0.002$), no association could be shown with OSA severity; $r=-0.02$ ($P=0.57$).
In a multiple linear regression analysis IGF-1 was predicted by age (coefficient 0.459, $P<0.001$) and BMI (coefficient -0.461, $P=0.027$), but not by OSA severity, gender, or presence of diabetes. OSA severity was predicted by BMI (coefficient 0.027, $P<0.001$), gender (coefficient -0.45, $P<0.001$) and age (coefficient 0.01, $P=0.005$), but not by IGF-1 or presence of diabetes.
Conclusion
Serum levels of IGF-I are dependent not only on age, but also BMI, with IGF-I being lower with increasing BMI. No significant effect of OSA on IGF-I levels could however be determined.

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P273

Cyclooxygenase-2 is a potential target for the treatment of Adamantinomatous craniopharyngioma

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Adamantinomatous craniopharyngiomas (ACPs) are among the most common intracranial tumours in children and they originate from undifferentiated pituitary progenitors. Mutations in the gene encoding for β-catenin (*CTNNB1*), which lead to the constitutive activation of the Wnt/β-catenin signalling pathway, have been associated with ACP. These tumours can invade adjacent structures, such as the hypothalamus, which makes complete resection difficult, leading to a high rate of recurrences and co-morbidities associated to the treatment. No pharmacological treatment currently exists for this condition. To identify new possible targets, we used microarray analysis to compare gene expression of pituitaries isolated from *WT* mice and from our mouse model of ACP. Our microarray data showed up-regulation of the cyclooxygenase-2 (COX-2)-encoding gene (*Ptgs-2*) in the ACP samples. COX-2 has been associated with poor prognosis in cancer and COX-2-inhibitors have been indicated as potential anti-cancer agents. To assess whether valdecoxib, a COX-2-selective inhibitor, also affects the activity of the Wnt/β-catenin signalling pathway, we used the Wnt-signalling reporter assay TOPFlash in a HEK-293T cell line treated with valdecoxib. Importantly, valdecoxib effectively repressed β-catenin transcriptional activity in a dose-dependent manner (up to 99% reduction compared to the control, $n=3$ in triplicate). In addition, our immunofluorescence analysis revealed for the first time COX-2 expression in the pituitary progenitors/stem cells (PPSCs) isolated from WT and ACP-mice. Notably, one week-treatment with valdecoxib of PPSCs isolated from murine ACP samples significantly impaired the proliferation capacity of the progenitors *in vitro*. In conclusion, we show for the first time that valdecoxib, a highly-selective COX-2-inhibitor, has also a highly inhibitory effect on the Wnt-canonical pathway signalling, hence reducing the proliferation and clonogenic potential of ACP-progenitor cells *in vitro*. Therefore, our data suggest that valdecoxib represents a promising candidate for novel and efficacious treatments for ACP.

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A comprehensive analysis of the AIP mutation positive pituitary tumour microenvironment: role of stromal cells and the pro-inflammatory cytokine network

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Introduction
The tumour microenvironment significantly influences tumour behaviour. Little is known about the pituitary adenoma microenvironment. *AIP* mutation positive (*AIP*pos) patients develop often aggressively growing pituitary tumours and the study of their microenvironment might identify factors leading to this aggressive phenotype which could help predict tumour behaviour and identify novel therapeutic targets.
Aim
The aim of this study was to extensively investigate the tumour microenvironment and discover its potential role in *AIP*pos tumourigenesis.
Methods
We have evaluated the expression of macrophages (CD68), T-reg cells (FOXP3), cytotoxic T cells (CD8), memory T cells (CD45RO) and vascular structures (CD31) as well as CCL5 and Fli-1 by immunohistochemistry on *AIP*pos and sporadic tumours. Stable *AIP*-knockdown pituitary somatotroph cells (GH3_AIP_KD) was used to study tumour-stromal cross-talk. Pituitary samples of a pituitary-specific *AIP*-knockout mouse model (AipFlox/Flox;Hesx1Cre/+) were also studied for macrophage cells.
Results
Immunohistochemical analysis revealed significantly increased levels of CD68+ macrophages ($P=0.01$), FOXP3+ T-reg cells ($P=0.009$) and vascular elements ($P=0.02$) in *AIP*pos tumours compared to sporadic somatotrophinomas. No differences were found in CD8 and CD45RO staining. GH3_AIP_KD cells attracted increased macrophage migration compared to non-targeting controls *via* the CCL5/CCR5 pathway. *AIP*pos tumours also showed higher levels of expression of pro-inflammatory cytokine CCL5 ($P=0.001$) and its regulatory transcription factor Fli-1 ($P=0.003$). Furthermore, the level of macrophage infiltration was increased in the pituitary-specific AIP-knockout pituitary samples, similar to human *AIP*pos tumours.
Conclusions
Using molecular markers, *in vitro* and *in vivo* models we have revealed that *AIP*pos tumours have a unique microenvironment which is strikingly different compared to sporadic somatotrophinomas. It appears that *AIP* deficiency in pituitary cells drives aggressive tumourigenesis partially *via* increasing immune cell infiltrates. Therefore, new treatments targeting the tumour microenvironment may have potential for the management of patients with aggressive *AIP*pos pituitary tumours.

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Long-term safety of gamma knife radiosurgery (STRS) for acromegaly

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Introduction
Incompletely controlled acromegaly has a three-fold excess all-cause mortality, with stroke being the predominant cause of death. Debate exists about the relationship between fractionated radiation (FRT) and risk of stroke, with radiation damage to cerebral vasculature potentially being a cause. We present outcomes in patients treated by gamma knife STRS at the National Centre for Stereotactic Radiosurgery in Sheffield, with 30-year follow-up.
Methods
118 patients with acromegaly underwent STRS in Sheffield between 1985 and 2015. Morbidity data were collected using notes review and direct patient or physician contact. NHS database and national death register provided date and cause of death where applicable.
Results
Of 118 patients, complete data is currently available on 64. Median follow up was 108 months (range 30–363). There were 5 deaths: three due to lower respiratory tract infections; one due to Idiopathic pulmonary fibrosis; and one due to cardiac arrhythmia. Too few deaths precluded calculation of Standardised Mortality Ratios. Median age at death was 65 (32–82) years and median follow-up post STRS at death was 103 (44–168) months. Of those who had not undergone prior FRT 18/48 (37.5%) developed new hypopituitarism. There were four cases of ophthalmoplegia, two of whom received prior FRT and two STRS treatments. All four cases had tumours invading the cavernous sinus. One patient developed worsened visual acuity (STRS prior to MRI-targeted therapy in 1993). There was one case of an anterior circulation stroke (at age 80), at 7 years post STRS with no prior history of FRT. Three patients required further pituitary surgery; two further radiation treatment.
Conclusion
This is the longest reported follow-up of any cohort of patients with acromegaly treated by gamma knife, specifically assessing morbidity and mortality. Stroke risk appears to be low following STRS. Second radiation treatment and cavernous sinus invasion may increase risk of ophthalmoplegia.

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P276

Adherence to Growth Hormone Therapy in Patients with Growth Hormone Deficiency Following Traumatic Brain Injury

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Background
Growth hormone deficiency (GHD) is an increasingly recognized potential consequence following traumatic brain injury (TBI). Outside of a formal, blinded RCT to demonstrate treatment effects, long term adherence to hGH replacement in a full reimbursement setting may serve as a pragmatic indicator of patient-perceived therapy benefits. Our objective was to evaluate adherence to therapy at one year for patients with GHD secondary to TBI in a full reimbursement setting.
Methods
We conducted a retrospective chart review of patients evaluated for GHD at the TBI clinic (>1 year post TBI) and referred to endocrinology for GH stimulation testing with insulin tolerance test (ITT) or glucagon stimulation test (GST) since December 2013. We obtained patient demographics, severity of TBI, baseline and post therapy IGF-1 level, data pertaining to pituitary hormone deficiencies, result of GH stimulation testing, and adherence to GH at one year follow-up from GH initiation. Adherence to therapy was defined according to the presence or absence of patient-initiated clinic follow up visits, a requisite step for ongoing hGH prescriptions.
Results
64 patient charts were reviewed. 48 patients had mild TBI, 6 had moderate TBI, 8 had severe TBI, and 2 patients had a non-traumatic etiology of brain injury. 42 patients underwent ITT or GST, and 27 patients were confirmed to have GHD. At the time of analysis, 20 patients had been started on GH therapy 1 year ago or longer. Of these patients, 11/20 returned for follow-up to continue GH replacement beyond one year, while 9/20 did not return for GH renewal beyond three months.
Discussion
In a full reimbursement setting, adherence to hGH replacement therapy at one year is modest, suggesting that GH replacement may not provide significant symptomatic benefit in many patients with GHD from traumatic brain injury.

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P277

Copeptin during hypertonic saline infusion in a polyuria/polydipsia syndrome case series

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Introduction
Copeptin is the C-terminal fragment of proAVP and provides an alternative measure of AVP secretion. While direct measurement of AVP during hypertonic saline infusion has been recommended as a diagnostic test for diabetes insipidus (DI), the number of reports examining the utility of copeptin in this context is limited. Here we describe a series of cases where measurement of copeptin during saline infusion has contributed to the diagnosis of patients with polyuria/polydipsia syndrome.
Methods
Biochemical and clinical data were collated for 9 cases where copeptin was measured during hypertonic saline infusion for the investigation of polyuria/polydipsia. Data collected included random serum and urine osmolality, serum copeptin and osmolality during saline infusion, other endocrinology tests, pituitary imaging and clinical presentation/history. The final diagnosis made by a Consultant Endocrinologist in view of all test results and clinical presentation was also recorded.
Results
A diagnosis of primary polydipsia was made in 6 cases. In these cases the maximum serum copeptin concentration during saline infusion was between 9.0 and 28.0 pmol/L. A diagnosis of central DI was made in a further 2 cases. In these 2 cases the maximum serum copeptin during saline infusion was <2.3 pmol/L. In the final case the differential diagnosis after both water deprivation/ddAVP challenge and hypertonic saline infusion was between primary polydipsia and partial nephrogenic DI. In this case the maximum copeptin during saline infusion was much higher than in the cases of primary polydipsia at 125 pmol/L, suggesting a degree of AVP resistance.
Conclusions
The results of this small case series demonstrate the potential of serum copeptin under osmotic stimulation as a diagnostic test for DI. Additional data is being collated to further determine the diagnostic performance of the hypertonic saline infusion test with copeptin measurement. This test has potential advantages over the conventional water deprivation test.

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P278

Pituitary function and quality of life in patients taking oral or transdermal opioid analgesics for non-cancer pain

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Background
Opioid analgesics are commonly used for chronic non-cancer pain but may impair gonadal and adrenal axis function. We measured pituitary function, rates of hormone deficiency, sexual function and quality of life (QoL) in patients on oral or transdermal opioids versus age and sex-matched controls.
Methods
Participants with chronic non-malignant pain receiving oral or transdermal opioids for more than six months and matched controls provided morning (before 0900 h) blood samples and completed validated questionnaires for general health, sexual function, fatigue and quality of life. Participants with morning serum cortisol levels <250 nmol/L underwent 250 μg short Synacthen test (SST) and overnight metyrapone test (OMT).
Results
Forty patients treated with opioids (M:25, F:15) and 25 age matched controls (M:14, F:11) were studied. BMI was significantly higher among the opioid users ($P<0.01$). There was no difference between opioid users and controls in mean morning cortisol in the overall group or testosterone among the men. However opioid users had a significantly higher rate of adrenal insufficiency (AI) defined by morning cortisol <250 nmol/L AND failing either the SST or OMT 9/40 vs 0/25

$P=0.01$. Median morphine equivalent daily dose was higher in opioid users with AI (100 mg vs 60 mg, $P<0.05$). There was a significant negative correlation between BMI and serum testosterone among male participants ($R=-0.50$, $P=0.001$). Multiple regression analysis showed a significant effect of BMI ($P=0.002$) but not opioid use ($P=0.29$). However, there was a small sub-group of male opioid users ($n=6$) whose testosterone lay below the expected level for BMI. Opioid treated patients scored significantly lower on all QoL and sexual function measures.

Conclusion

A significant proportion of oral/transdermal opioid users are at risk of adrenal insufficiency. BMI confounds assessment of testosterone deficiency. Further data are required to determine optimal management strategies, including opioid reduction, opioid rotation, or hormone replacement.

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P279

Bilateral Inferior Petrosal Sinus Sampling (BIPSS) reliably differentiates pituitary from ectopic Cushing's syndrome, but does not predict pituitary tumour location, especially when lateralizing to the right

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Background

BIPSS is considered the gold-standard procedure for differentiating autonomous pituitary [Cushing's Disease (CD)] and ectopic ACTH syndrome (EAS) sources of ACTH hypersecretion. A basal (i.e. unstimulated) pituitary:peripheral ACTH ratio >2, and/or a CRH stimulated pituitary:peripheral ACTH ratio >3, have been proposed as indicative of CD, with a range of sensitivities and specificities cited in the literature. Additionally, in CD a peak interpetrosal gradient of >1.4 has been reported to predict the side of the adenoma in approximately 2/3 of cases. We have re-examined the accuracy of these diagnostic thresholds in a cohort of patients undergoing BIPSS in our centre over the last 12 years, in whom confirmation of the underlying diagnosis was subsequently established.

Methods

41 patients with biochemically proven ACTH-dependent Cushing's syndrome, who had undergone BIPSS and had either subsequent histological confirmation of the ACTH source or significant improvement/cure of their Cushing's were included in the study.

Results

Based on pre-CRH stimulation results, 90% of patients were deemed to have pituitary Cushing's and 10% EAS. Post-CRH stimulation, 95% of patients reached the cut-off for CD. These yielded a sensitivity of 97% and a specificity of 100% for pre-CRH stimulation and 100% sensitivity and 67% specificity for post-CRH stimulation. The majority of BIPSS procedures lateralized to the right side (65%), but at surgery this was found to be correct in only half of cases. On the contrary, left lateralization had a much higher positive predictive value (80%). Overall, lateralization was accurate in 60% of cases.

Conclusion

Predominance of right sided lateralization on BIPSS is frequently (1:2) misleading. We propose that additional localizing strategies are pursued prior to pituitary surgery, such as detailed MRI sequences (e.g. SPGR MRI) or functional imaging modalities (e.g. ^{11}C-Methionine PET). Whole gland exploration is particularly important for patients with inconclusive pre-operative localizing investigations.

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P280

Pituitary radiotherapy causes increased, cardio- and cerebrovascular morbidity, and high Age Standardized Mortality Ratio (ASMR): single centre experience

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Background

Pituitary radiotherapy (RT) is known to have metabolic, cardiovascular and cerebrovascular complications due to the effects of radiation on normal pituitary tissue and surrounding neurological structures.

Objectives

Retrospective evaluation of effects of RT on pituitary dysfunction, type 2 diabetes mellitus, cardio- and cerebrovascular morbidity and mortality in unselected consecutive pituitary adenomas in a tertiary centre.

Methodology

Retrospective case note and electronic record review of 124 consecutive pituitary adenomas (Non-functioning adenomas {NFA}-57, acromegaly-33, prolactinoma-8, cushings-6, others-6) subjected to RT from 1968 to 2015 was undertaken. Age Standardised Mortality Ratio (ASMR) was calculated in comparison with mortality rates of Leicestershire population as per Office of National Statistics (ONS).

Results

$n=124$ (68 males, 56 females), mean age 45 yrs, mean duration of follow-up post-RT 16.2 yrs. 53% of functional tumours achieved remission (25/47). Hypopituitarism increased from 39% pre-RT (48/124) to 81% (100/124) by the end of follow-up period. An increased prevalence of ischaemic heart disease (IHD)(7 to 11), myocardial infarction (1 to 5), stroke (1 to 12), heart failure (1 to 9), dementia (1 to 6) was noted from pre-RT to end of follow-up period. There was an approximate 5-fold increased incidence of diabetes (6 to 29), and one new diagnosis of tumour (meningioma). Acromegaly patients showed higher IHD incidence than NFA (16% vs 10%); NFA showed higher stroke incidence than acromegaly (14% vs 3%) . ASMR was 8113/100,000 (CI 5345 – 10882 deaths per 100,000 population) for RT versus ASMR for Leicestershire 1174/100,000 (reported from ONS), yielding a Relative Risk of 6.9.

Conclusion

RT-induced-hypopituitarism occurs in the majority of patients. RT appears to increase the incidence of diabetes; stroke, cardiac disease and dementia. In post-RT patients, ASMR is $\simeq 7$ times higher than the background population. These data suggests a conservative approach to pituitary RT should be considered in order to prevent long term morbidity and mortality.

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P281

Comparison of Overnight Dexamethasone Suppression Test with Low Dose Dexamethasone Suppression Test for the Diagnosis of Cushing's Syndrome

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Introduction

Current guidelines from The Endocrine Society indicate that 2 different tests from urinary free cortisol (UFC) measurement, salivary cortisol (SC) measurement, low-dose dexamethasone suppression test (LDDST) or overnight dexamethasone suppression test (ODST) are required to diagnose Cushing's syndrome (CS). The low-dose dexamethasone test (LDDST) is often used as the confirmatory test when diagnosing CS. The overnight dexamethasone suppression test (ODST) is often utilised as a screening test for CS, and is faster, cheaper, and easier to perform than the LDDST. This study aims to determine the level of concordance between the LDDST and ODST.

Subjects and Methods

This is a retrospective cohort study, analysing results from September 2005 - April 2017 in two tertiary care centres, for patients who had undergone an ODST, UFC measurement, or late-night SC measurement, in addition to a LDDST. Concordance and Cohen's kappa coefficient were calculated for comparison of all tests. The level of correlation between final serum cortisol concentration of the LDDST and ODST was determined using Pearson's correlation coefficient ($P\leq 0.05$).

Results

43 patients were included in the study. Concordance was shown between all tests. The LDDST was 89.2% concordant with the ODST, with a kappa coefficient of 0.549. The final serum cortisol concentrations of the LDDST and ODST showed a significant positive correlation, with a Pearson's correlation coefficient of 0.82 ($P\leq 0.05$).

Conclusion

The ODST has the potential to replace the LDDST as the confirmatory test for CS diagnosis, especially when existing literature regarding sensitivity and specificity is reviewed.

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P282

Understanding the psychosocial needs of pituitary patients: a survey of Pituitary Foundation members

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Background
Management of pituitary conditions is notoriously difficult and patients often experience high levels of distress which are often not addressed by health professionals. As a result, pituitary conditions have been found to have a large negative impact on quality of life. The aims of this study were 1) to identify the psychosocial symptoms associated with pituitary conditions, and 2) to identify any differences in symptomatology across different pituitary conditions, age ranges and gender.
Methods
A questionnaire was completed by 1062 members of the Pituitary Foundation (683 female, aged under 18 to over 65). With a format based on the Cancerbackup Survey (2006), the questionnaire was designed using material from the Pituitary Foundation Needs Analysis report (2006) and some relevant questions from other validated questionnaires. Respondents completed either a pen and paper or Survey Monkey version.
Results
Physical and psychosocial issues were identified, including mood swings, fatigue, anxiety and depression. The results identified significant variation in symptoms across gender, age range and condition type, particularly in relation to infertility and headaches, difficulties with sex life, appearance and pain management. E.g. headaches were associated with women, younger patients and those with prolactinoma, diabetes insipidus, acromegaly or hypogonadism. Difficulties with sex life were associated with men, younger patients, and those with craniopharyngioma or prolactinoma.
Conclusions
Participants were found to be experiencing a range of debilitating psychosocial and physical symptoms that were impairing long term functioning. These symptoms need further support in terms of patient information, advice and condition management.

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P283

Impact of menopause on the natural history of pre-existing prolactinomas

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Background
It has been proposed that menopause has a beneficial effect on the natural history of hyperprolactinaemia attributed to prolactinoma. Nonetheless, series systematically assessing outcome in females with prolactinoma who have passed through menopause are very limited.
Aim
To investigate the impact of menopause on prolactinomas in patients not on dopamine agonist (DA) treatment.
Patients and Methods
Women with a prolactinoma diagnosed before the cessation of menses and who after menopause were off DA were identified from the Departmental database. Clinical, biochemical and imaging data were collected.
Results
Thirty-two patients were identified (median age at diagnosis 33.5 years, range 16-49, 24/8 micro-/macroadenomas). DA was stopped peri-/post-menopause in 28 and before menopause in 3; one patient diagnosed in the peri-menopausal period had not been offered DA treatment. Before stopping the DA, 23/31 (74%) women had normal PRL and in 11 there was no evidence of adenoma on imaging (for 4 patients imaging data close to DA discontinuation were not available and in the remaining ones there was visible adenoma). Median follow-up (from discontinuation of DA until last prolactin measurement) was 3 years (0.5–29). At latest assessment, prolactin was normal in 16/32 (50%) (13 had micro- and 3 macroadenoma at diagnosis). 7/23 (30%) women with normal prolactin at discontinuation of DA had hyperprolactinaemia at latest evaluation; 1/9 (11%) with hyperprolactinaemia at discontinuation of DA had normal prolactin at last assessment. Two patients (both with microadenoma) showed gradual increase in the prolactin values (43.3% and 73.6% increase of values of latest measurement in comparison to those one year after stopping DA), and in one of them, increase in the adenoma size was confirmed.
Conclusions
Following menopause, nearly half of women with prolactinoma will have hyperprolactinaemia after discontinuation of DA (median follow-up 3 years). Adenoma enlargement can occur rarely, necessitating monitoring of the serum prolactin.

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P284

Non-functioning pituitary macroadenomas: characteristics and outcomes following endoscopic trans-sphenoidal surgery – a single UK tertiary referral centre experience

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Background
Non-functioning pituitary adenomas (NFPA) account for 30-35% of pituitary adenomas. They can lead to hypopituitarism and visual field defects. Trans-sphenoidal resection of pituitary adenoma remains the treatment of choice.
Methods
We compared clinical, biochemical, and imaging characteristics of NFPAs at presentation with post-surgical outcomes in a retrospective cohort study. Patients who underwent endoscopic trans-sphenoidal resection for a non-functioning pituitary macroadenoma (July 2009 – August 2016) were identified and clinical records analysed.
Results
118 patients with NFPAs were included (64% male, follow-up 3.3 ± 1.8 yrs, age at surgery 59.7 ± 13.6 yrs). Immunohistochemical analysis identified most tumours to be gonadotroph ($n=55$, 46.6%) or null cell ($n=53$, 44.9%) adenomas. At presentation, 52 patients (44%) had normal pituitary function; 47 (39.8%) 1–2 anterior pituitary axis deficits and 19 (16.1%) ≥ 3 deficits. Gonadotroph deficiency (43%) was most frequent. Male gender (65% vs. 44%, $P=0.0008$) and older age ($P=0.02$) were associated with multiple hormone deficiencies.
Pre-operative tumour volume did not correlate with degree of hypopituitarism ($P=0.35$, $R=0.09$). Mean tumour volume reduction after surgical resection was $73.1 \pm 23.2\%$.
At follow-up, the number of patients with hormone deficiencies increased from 55.9% to 66.1% after surgery. Six patients developed permanent diabetes insipidus. Extent of tumour resection was not predictive of new onset hypopituitarism post-operatively ($P=0.14$). Overall, postoperative hormonal recovery was observed in 14 patients (11.8%), with the greatest recovery occurring in the gonadal axis (57.1%, 8/14).
Thirty-two patients (27.1%) were submitted to radiotherapy whilst 15.3% ($n=18$) underwent redo-surgery. A large residual tumour volume increased the likelihood for adjuvant radiotherapy (4.25 vs. 1.34 cm^3, $P=0.04$), but was not predictive of need for repeat surgery ($P=0.11$).
Conclusions
NFPA prevail in males and they are more likely to have multi-hormonal deficits. In our cohort, total/subtotal resection of pituitary adenoma is not a significant risk to pituitary function and it possibly can promote recovery of pre-existing pituitary dysfunction, in particular in gonadal axis.

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P285

Prevalence of paraganglioma at first screen in SDH mutation carriers identified through family screening

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Introduction
Mutations in the succinate dehydrogenase gene (SDH) predispose to the development of paraganglioma (PGL) which arise from parasympathetic and extra-adrenal sympathetic-associated chromaffin tissues. Identification of an index case results in family 'cascade' screening, often of asymptomatic individuals.
Aims
To identify prevalence of PGL tumours and elevated plasma metanephrines at first screening in patients newly identified as carrying a pathogenic SDH mutation.
Methods
Data collection from a database of patients with SDH mutations at Guy's and St. Thomas's NHS Foundation Trust. Following confirmation of a pathogenic SDH mutation all patients had measurement of plasma metanephrines and whole-body (incl. head & neck) MRI.
Results
35 adult patients (mean age 39 years; range 10–66) were included. All were asymptomatic and identified as carrying a mutation in SDH through family screening (3 with SDHA, 24 with SDHB, 3 with SDHC and 5 with SDHD). Using MDM records initial biochemical and cross-sectional screening results were obtained. 10 of 35 patients (29%, 5 with SDHB mutation and 5 with SDHD mutation) had a tumour at initial screening. Tumour locations were as follows; 4 head and neck (3×SDHD, 1×SDHB), 5 abdominal (2×SDHD, 3×SDHB) and 1 thoracic (SDHB). 4 patients had elevated metanephrines at initial screening (11%), one of whom had a malignant tumour detected 6 months from initial screen in the thorax (SDHB mutation).
Conclusion
The tumour burden is high (29%) in these adult patients with SDH mutations at initial screening. Tumours were located in the head & neck, abdomen and mediastinum. Not all abdominal tumours were associated with demonstrable catecholamine excess.

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P286

Acromegaly complication screening – are we meeting the guidelines?

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Aims
Endocrine Society (ES) acromegaly guidelines (2014) addressed complication screening. Uncontrolled acromegaly is associated with elevated cardiovascular mortality due to risk factors including hypertension (HT), diabetes mellitus (DM), obstructive sleep apnoea (OSA), and with an increased risk of colorectal cancer and polyps among other types of neoplasias. We audited our clinical practice with regards to acromegaly complication screening.
Methods
Retrospective study of all patients with acromegaly under active follow up in a teaching hospital. Data were collected from paper and electronic records (2009 onwards). Rates of complication screening were compared before and after the publication of the guidelines (2014).
Results
Fifty-one patients were included, 61% female. Mean age 58.9 ± 16.5 years. Mean age at diagnosis 43.4 ± 16.9 years. Median of follow up of 13 years, IQR:15.5. All patients were screened for HT and DM at diagnosis, and 93% and 98% during the last year respectively. Currently 19 (37%) of patients have HT and 13 (26%) have DM, impaired fasting glucose/impaired glucose tolerance. See Table 1 for comparison of complication screening pre and post guidelines. Twenty-six (51%) patients have had a colonoscopy done, median age at colonoscopy of 54 years, IQR:19.7; this was done in a median of 7 years after diagnosis IQR:9.7. Twenty (77%) had a normal result, 6 (23%) were reported to have polyps. 5 out of 6 patients referred to the sleep apnoea clinic were diagnosed with OSA.
Comments
The ES guidelines have enhanced our awareness of screening for complications in patients with acromegaly. Referral for colonoscopy and screening for OSA has increased, but there is scope for improvement for thyroid examination. The ES guidelines differ from British Society of Gastroenterology (2009) guidelines in recommending colonoscopy screening commence at diagnosis rather than at age 40.

Table 1 Influence of guidelines on complication screening rates

	Before guidelines	After guidelines
Colonoscopy – had or referred	33%	84%
Enquired regarding snoring	40%	64%
OSA-Epworth score completed	2%	60%
Thyroid examination	14%	22%

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P287

Inpatient endocrinology referrals: does the RCP report 'Referring Wisely' describe who should be referred?

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The Royal College of Physicians (RCP) published a report called Referring Wisely in June 2017. The report asked specialty physicians for a short list of conditions they felt would benefit from specialist input in the context of acute inpatient management (recommended referrals). It also asked for a list of conditions which need not be referred (avoid referrals).
Methods
We retrospectively audited inpatient referrals from our electronic inpatient referral system. The indication for referral was then checked against the RCP criteria for referral.
Results
43 inpatient referrals over one month were identified. These referrals related to 37 patients (6 duplicate or re-referrals). 89% (33/37) of referrals were in the recommended category. Zero (0/37) were from the avoid referral group. Four other referrals were unclassified and these were: suspected Cushing's, diabetes insipidus, suspected pheochromocytoma and 'funny' TFTs (Table 1).
Conclusion
The audit demonstrates that current referral patterns are almost completely in line with the RCPs recommendations. Proposed adaptations to RCP list would include:

- Diabetes insipidus, suspected pheochromocytoma and suspected Cushing's could be included as recommended referrals.

Table 1

	Referral criteria	Number (total = 37)
RCP recommended referral	Hyponatraemia (severe or symptomatic)	14
	Thyrotoxicosis	5
	Adrenal insufficiency	5
	Thyroid/adrenal/pituitary mass	5
	Hypocalcaemia	4
	Amenorrhoea/hypogonadism	0
Other referrals	Cushing's, DI, suspected pheo, odd TFTs	4

- Amenorrhea/hypogonadism could be removed from the list of inpatient recommended referrals.
- Adrenal insufficiency category could be adapted to include hypopituitarism.

Assessment of the impact and outcomes of inpatient endocrine referrals is the subject of future work.

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P288

Post-surgical treatment outcomes of acromegalic patients

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Objective
Various treatment modalities are used for acromegalic patients to normalise growth hormone and IGF-1 values to those matched with the normal population in order to normalise morbidity and mortality. A retrospective audit was undertaken to review the treatment outcomes of four therapy groups. 1. Surgery alone, 2. Surgery and radiotherapy, 3. Surgery, radiotherapy and adjunct therapy, 4. Surgery and aduct without radiotherapy.
Methodology
66 patients were recruited with a mean follow up period of 11.6 years. All patients had undergone transspenoidal surgery as part of their clinical management. Outcome measures were classified as cure/control or with active disease measured by their last available IGF-1 value. Comparisons were made with the four groups concerning pre and post IGF-1 values, tumour size, tumour extension and presence of residual tumour in relation to outcome.
Results
Overall, 62% were cured or controlled. 20% were treated with surgery alone, 9% had surgery and radiotherapy, 45% had a combination of surgery and other therapies and 26% had surgery, adjunct therapy but no radiotherapy. Surgery alone resulted in cure for 77%. Disease control was evident in: Surgery and radiotherapy 50%, combined therapy including radiotherapy 60% and combined therapy without radiotherapy 59%. Of the 73% patients with residual disease, 37% continued to have active disease. 44% patients had tumour extension, 45% with active disease. Post-operative IGF-1 was significantly different to pre-operative levels. The most prevalent co-morbidity was hypopituritism followed closely by ACTH deficiency in 48% of patients. Data showed that there was a trend for ACTH deficiency in the two groups treated with radiotherapy but failed to reach significance.
Conclusion
This audit has shown as expected that there is a significant improvement in IGF-1 post treatment when compared to pre-treatment values in all groups. No relationship was found between residual disease, tumour size or tumour extension with outcome. However, the high prevalence of ACTH deficiency is a serious co-morbidity with little published data on this to date.

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P289

Treating mild central hypothyroidism in postoperative pituitary patients – impact of Endocrine Society guidelines

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Aim
Endocrine Society (2016) published guidelines for hormonal replacement in hypopituitarism. Central hypothyroidism (CH) is defined as fT4 below reference range and mild CH is defined as fT4 in the low-normal range with suggestive symptoms in the context of pituitary disease. In patients with panhypopituitarism levothyroxine in doses sufficient to achieve fT4 levels in the upper half of the reference range is recommended. In our centre fT4 normal range is 10–25 pmol/L. We audited our current clinical practice regarding levothyroxine replacement in patients post trans-sphenoidal surgery (TSS).
Method
Retrospective study of patient's who underwent TSS from Jan'13 – Feb'17 at a teaching hospital. Data were collected from electronic records.
Results
Sixty patients were included (31 male). Mean age 59 ± 15.6 years. Forty-two patients underwent TSS for non-functioning adenomas (NFA), 8 for Acromegaly, 6 for Cushing's disease and the rest due to other reasons. Pre-operatively 9 (15%) patients were on levothyroxine replacement, 7 of whom had secondary hypothyroidism. At the time of audit (April 2017), 36 (60%) patients were on levothyroxine, 26 of these were on additional hormonal replacement. One patient was on GH replacement alone with low-normal fT4 levels. Following the guidelines, 11/18 patients on levothyroxine had mild CH symptoms and as fT4 was in the lower half of normal range their dose was increased. 6/22 patients not on thyroid replacement had symptoms of mild CH with fT4 in lower half of normal range and were commenced on levothyroxine. Twelve patients on levothyroxine had fT4 in the top half of normal range.
Conclusions
The new guidelines have made us more vigilant with regards to levothyroxine replacement in patients with mild CH following TSS. Levothyroxine treatment in those patients with possible CH is clinician dependant. GH should not be started prior to correcting other hormone deficiencies including mild CH considering relative cost of therapies.

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P290

An assessment of hypothalamus-pituitary-adrenal axis post-pituitary surgery: can day 8 morning cortisol predict normal SST?

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Background
Short Synacthen test (SST) is commonly used for the assessment of the hypothalamus-pituitary-adrenal (HPA) axis after pituitary surgery. In our centre, patients are discharged on hydrocortisone on day 3 post-surgery and 9am cortisol on day 8 post-surgery is measured. Hydrocortisone is stopped if cortisol is ≥ 350 nmol/L on day 8. Six weeks post-surgery SST is performed and treatment adjusted. We aimed to assess the performance of day 8 morning cortisol as a predictor of the hypothalamus-pituitary-adrenal (HPA) axis status in patients who underwent transsphenoidal surgery (TSS).
Methods
We have performed a retrospective cohort analysis of 79 patients who had a TSS for non-ACTH producing pituitary tumours in Oxford between 2014 and 2017 and had 6 weeks post-surgery SST data available. Cortisol was measured using Advia-Centaur assay (Siemens). SPSS v23 was used for statistical analysis.
Results
ROC curve analysis was performed to identify a 9am cortisol value at day 8 post-TSS to predict accurately passing the SST at 6 weeks post-surgery. 9am cortisol above 433 nmol/L at day 8 had 100% specificity for predicting a normal SST at 6 week post-surgery. Our current day 8 cortisol cut-off of 350 nmol/L had 85% specificity for passing 6 week post-surgery SST, therefore 15% of patients would stop hydrocortisone inappropriately.
We also compared SST data pre- and post-TSS ($n = 61$): 3 patients failed pre- and post-surgery SST (4.9%); 4 patients failed pre-surgery SST but subsequently passed 6 week post-surgery SST (6.5%); 10 patients had normal SST pre-TSS but failed 6 week post-surgery SST (16.4%).
Conclusions
In our cohort of patients, day 8 cortisol above 350 nmol/L led to discontinuation of steroids in 15% of cases who subsequently failed SST. Our results should be validated on an increased number of subjects aiming for a safe algorithm for post-TSS assessment of the HPA axis.

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P291

Predictors of post-operative hypopituitarism following transsphenoidal surgery

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Background & Aims
The aims of transsphenoidal surgery (restoration/preservation of vision and amelioration of hormonal excess) are balanced against the risk of inducing new post-operative pituitary deficits. This study aims to assess the rate of new anterior hormonal deficits following transsphenoidal pituitary adenoma surgery in our centre and to assess whether the visibility of normal pituitary gland on pre-operative imaging predicts this.
Methods
Patients undergoing first transsphenoidal surgery for a pituitary adenoma between 2012 and 2016 were identified. Pre-operative imaging was reviewed and the presence or absence of visible normal pituitary gland on MRI noted. Biochemical testing/medications pre-operatively and six weeks post-operatively were reviewed.
Results
Full data were available for 132 patients [71 male, 61 female, ages 14-87 yr (median 53 yr); 100 macroadenomas, 32 microadenomas; 61 non-functioning, 71 functioning (38 acromegaly, 13 Cushing's, 5 thyrotropinoma, 14 prolactinoma, 1 gonadotrophinoma)]. Of these, 37 had new deficits post-operatively (22 ACTH alone, 9 ACTH plus other hormones, 7 one or more other hormones without ACTH). The visibility of normal pituitary pre-operatively did not predict the development of post-operative axis deficits ($P=1.000$, Fisher's exact test). An interim analysis in 2014 noted that of 25 patients undergoing surgery in 2012, 10 had ACTH deficiency at six weeks post-op but at 4 months, 5 of these had recovered this axis (2 persisting ACTH-deficiency, 3 data at 4 months incomplete). Our routine practice in 2012 was to discharge all patients on full replacement hydrocortisone (10/5/5 mg/day). Since 2015 our practice has been to personalise hydrocortisone on discharge based on post-operative 9am cortisol (2^{nd} or 3^{rd} day post-op). In 2016, 4/30 patients had ACTH-deficiency at 6 weeks post-op.
Conclusions
Discharge hydrocortisone dosing after transsphenoidal surgery should reflect individual patient requirements to avoid (reversible) HPA axis suppression. The ability to visualise normal pituitary on pre-operative MRI does not predict post-operative hypopituitarism.

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P292

The burden of arthropathy in acromegaly: results from an observational study

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Introduction
Patients with acromegaly are often left with long-term sequelae, among which arthropathy is the most common. Studies have shown impaired quality of life (QoL) in patients with acromegaly, even after long-term remission. Arthropathy is a negative predictive factor of QoL, due to its impact on physical symptoms and functioning.
Patients/Methods
To characterise further the extent of the acromegalic arthopathy, we conducted an observation study on 62 patients with acromegaly. Participants were interviewed individually for the presence, distribution and severity of joint-related symptoms. Additionally, participants' medical records were reviewed and acromegaly-related data were collected.
Results
29 male and 33 female patients with acromegaly (mean age 55 ± 13 yrs) were recruited. 83.8% had pituitary surgery, 41.9% had radiotherapy and 85.5% received medical treatment. Mean duration of active disease and disease remission were 14.3 ± 10.0 yrs and 5.5 ± 7.6 yrs respectively. Based on biochemical criteria, 46.8% of patients had active acromegaly during the study, whereas 53.2% were in remission, which was achieved with or without long-term medical treatment.
88.7% of patients reported arthralgia (mean severity score 3.8 ± 2.8 on a 0–10 scale). The most commonly affected joint site was the knee (71%), followed by the small joints of the wrist/hand (51.6%) and the lower spine (45.2%). 79% of patients reported pain in >1 sites. Joint symptoms were bilateral in 83.8% of cases. 56.5% of patients required analgesia for arthralgia; 51.4% of them on a regular basis. 24.2% of patients had previously undergone joint surgery due to arthropathy (mean age of 51.2 ± 13.1 yrs). In 60% of those cases, patients required surgery in >1 joints.
Conclusions
Acromegalic arthropathy is a symmetrical polyarthropathy, affecting both the axial and appendicular skeleton and remains a major cause of morbidity in acromegaly. It may progress to a debilitating pathology, with patients requiring joint replacement at a relatively young age. Joint-related symptoms should be assessed regularly during clinic appointments. Future research should focus on developing strategies for prevention of the acromegalic arthropathy.

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P293

Cannulated prolactin avoids over-diagnosis and unnecessary investigations in normoprolactinaemic patients

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Objective
Hyperprolactinaemia is one of the most common disorders of the hypothalamic-pituitary axis. Endocrine Society guidelines state that a single prolactin measurement in a blood sample obtained at any time of day is adequate to confirm hyperprolactinaemia. However, prolactin levels can be confounded by physiological stimuli, e.g sleep, stress or exercise. Our objective was to assess the clinical significance of prolactin level obtained via cannulated prolactin test compared to a single non-rested prolactin sample obtained by venepuncture.
Methodology
A retrospective analysis was carried out for all patients referred to the Endocrine Department for hyperprolactinaemia and underwent cannulated prolactin test between June 2016–2017. A cannula was inserted and a 'cannulated prolactin' sample was withdrawn 60 minutes after bed-rest through the cannula. The prolactin on referral was used as the non-rested sample for comparison. Normal range prolactin <496 mIU/L.
Results
Thirty patients (23 female, 7 male) with a mean age ($+/-$SD) of 34.4 years ($+/-$ 7.3 years) were included. 13 out of 30 had no associated symptoms. Mean 'referral prolactin' was 796 mU/L ($+/-280$ mU/L) compared to mean 'cannulated prolactin' 400 mU/L ($+/-178$ mU/L). Only 8 out of 30 patients had true hyperprolactinaemia with elevated cannulated prolactin levels. Meanwhile, 22 out of 30 (73%) patients had normal cannulated prolactin measurements. Among the 22 patients with normal cannulated prolactin, 5 of them had MRI pituitary performed prior to referral and cannulated prolactin level taken and were reported normal.
Conclusion
Cannulated prolactin measurement is useful in excluding true hyperprolactinaemia in 73% of patients with high referral prolactin measurements. Furthermore our study suggests samples taken at 60 mins are sufficient for a resting cannulated sample to be taken. Undertaking a cannulated prolactin in such patients may considerably reduce the number of MRI scans performed.

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P294

Outcomes of endoscopic, endo-nasal, trans-sphenoidal pituitary adenoma surgery for Acromegaly and Cushing's disease: A single UK centre experience

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Background
Endoscopic trans-sphenoidal surgery is a technical advance for treatment of pituitary tumours. We present the outcomes of patients with Acromegaly or Cushing's disease undergoing selective pituitary adenomectomy in a regional neurosurgical centre.
Methods
Retrospective cohort study August 2010-August 2017. Imaging, histology and pituitary hormone assessments were collated pre and post-operatively to quantify patient hormonal outcomes.
Results
25 patients with Acromegaly or Cushing's disease underwent resection (13 Acromegaly and 12 Cushing's disease.)
Acromegaly group
- Mean age at surgery - 50.6 years
- 9 patients had no pre-operative hormone deficiency and 4 had a deficiency of 1 hormone. None had multiple hormone deficiencies.
- Post-operatively, at last follow up (mean follow up 38.25 months), 7 patients had no hormone deficiency, 2 were deficient in 1 hormone, and 2 in 2-3 hormones. 1 patient died (unrelated to surgery) and 1 lost to follow up.
- 2 patients required no further adjuvant therapy/surgery and 3 required repeat surgery, one of which was curative. Remaining patients (8) required a combination of radiotherapy and/or medical therapy.

Cushing's group
- Mean age at surgery - 43.5 years.
- 11 patients had no hormone deficiency pre-operatively and 1 patient had 1 hormone deficiency.
- Post-operatively, at last follow up (mean follow up 32.8 months,) 5 patients had no hormone deficiency, 5 an isolated hormone deficiency, 2 were lost to follow up.
- 6 patients required no further treatment. 3 required re-do surgery, 1 of which was curative. 3 patients needed medical adjuvant treatment.

Conclusion
We present the outcomes of patients following endoscopic trans-sphenoidal surgery for Acromegaly and Cushing's disease. The need for repeat surgery was low in both groups and when needed, it was not curative in 66% of cases.
There is no significant damage to pituitary gland function as a result of surgery.

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P295

Transitoin from paediatric to adult clinic in endocrinology: an assessment of experience at University College Hospital from the prospective of the adult service

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Background
Transition from paediatric to adult services is a crucial process for young adults with long term conditions (LTC) affecting quality of life and engagement with medical services. The recent NICE report has outlined overarching principles for an effective transition. This can be a challenge for paediatricians and adult physicians as both hospital sites and medical/nursing teams can change. There is a dearth of evidence regarding the effectiveness of the process.
Objectives
1. To audit the process of transition in a tertiary endocrine centre describing the current transition pathway and patients experiences versus NICE guidance.
2. To highlight achievable goals to improve our services.

Material and Methods
The medical records of 100 patients transitioning from paediatric to adult care in a dedicated endocrine clinic for young adults were reviewed for the following variables:
1. Referral information and diagnosis
2. Specific transition issues identified by the referrer
3. Discussion on transition at first consultation
4. Continuity of care
5. Encouragement of seeing patient alone
6. Discussion of psychosocial issues

Preliminary data from a focus group of 4 adults was assessed.
Results
Explanation of transition and continuity of care was universal. Full psychosocial discussions were reported in less than 8% of consultations. 20% of patients had incomplete referral documentation. Transition issues were documented in 51% of cases. The focus group highlighted the importance of continuity of care, receiving information about transition before the transfer, need for a patient passport and the psychology impact of LTC on young people.
Discussion
These data have highlighted a number of changes we can make immediately to our service. These include establishing contact with the young adult before the transfer, ensuring all aspects described above are discussed during consultations as well as encouraging patient's independence.

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P296

Connected, supported, informed: experiences & benefits of membership of the pituitary foundation

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Background
Pituitary conditions have been found to have a significant impact on quality of life. As such it is important that patients have access to support services to ensure their ongoing physical and psychological needs are met. The aim of this study was to explore the experiences of patients with pituitary conditions who are members of the Pituitary Foundation to better understand how the Foundation supports their needs.
Methods
A series of qualitative interviews were conducted with 10 self-selected members of the Pituitary Foundation (four male, six female; aged 37 to 72 years) about their conditions, their needs and their experiences with the Foundation. Data were analysed using thematic analysis. Secondary thematic analysis was conducted on a wider sample of 935 members of the Pituitary Foundation.
Results
The main issue requiring support was the life-changing nature of a pituitary diagnosis. Themes specific to the Pituitary Foundation identified it as an important source of support, although there were issues in finding out about and accessing it. Local support groups were particularly highly valued, but these do not exist in all locales.
Conclusions
Participants clearly valued the Pituitary Foundation as a vital source of support and information when trying to make sense of and manage their pituitary condition. Better training is required for health professionals about pituitary conditions and their long term consequences, and the need to signpost patients to wider services at the point of diagnosis.

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P297

Recurrence rate of hyperprolactinemia after dopamine agonists withdrawal in macroprolactinoma patients

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Background
Dopamine agonists (DA) have excellent result in controlling both hyperprolactinemia and tumor volume in macroprolactinomas. However, even after long term DA treatment, withdrawal of dopamine agonists results in recurrence of hyperprolactinemia in a significant proportion of patients.
Aim
To assess recurrence rate of hyperprolactinemia after DA withdrawal in a large series of patients treated in a tertiary endocrine center.
Patients and methods
43 patients with macroprolactinomas, treated with DA for at least 2 years, fullfilled the criteria for DA withdrawal: normal serum prolactin (PRL) on minimal DA dose, no visible tumor on MRI/computed tomography or tumor maximum diameter $\leq$10 mm. PRL was measured by chemiluminecense. Pituitary imaging was performed by computed tomography scan or MRI.

Results
In 18 patients (41.9%) hyperprolactinemia recurred; all reccurences occured in the first year after DA withdrawal, and the majority in the first 6 months. 25 patients (58.1%) showed persistent normal prolactin levels for more than 12 months (median 28 months) after DA withdrawal and were considered curred. In two patients, first attempt to withdrawal DA treatment failed, while the second attempt lead to long term normoprolactinemia.
Conclusion
There is a high rate of recurrence of hyperprolactinemia in macroprolactinomas after DA withdrawal. However, half of patients showed normal prolactin long time after DA withdrawal. A trial of DA withdrawal should be offered to patients responsive to long-term DA treatment with no visible tumor on imaging.

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P298

Diagnostic challenges in Cyclical Cushing's syndrome presenting with Bilateral Central Serous Retinopathy

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Case summary
A 55 year-old lady was referred by ophthalmology following diagnosis of bilateral central serous retinopathy, an accumulation of sub-retinal fluid at the fundus associated with Cushing's syndrome. She also had proximal myopathy, bruising, centripetal weight gain and hypertension. Cushing's was confirmed by 1 mg overnight DST (cortisol 581 nmol/L) and 48 hr-LDDST (407 nmol/L). 24 hr UFC was raised at 2666 nmol/L (12–486). The initial ACTH was low at 5 ng/L, but CT adrenals was normal. When re-measured five months later, ACTH was raised at 27.6 and 40.4 ng/L. Pituitary MRI showed a possible 2.5 mm microadenoma and CT chest was normal. Later inferior petrosal sinus sampling (IPSS) showed a central:peripheral ACTH gradient and was interpreted to exclude an ectopic source of ACTH. She underwent transsphenoidal hypophysectomy on two occasions, but histology showed no evidence of corticotroph adenoma. After the second surgery there was normal response to dexamethasone suppression. However postoperative imaging confirmed residual pituitary tissue and, besides persistent diabetes insipidus, other pituitary hormone secretion was intact. Four months later, 1 mg dexamethasone suppression was again abnormal (cortisol 211 nmol/L), but after only three weeks cortisol suppressed on 48 hr-LDDST ($<$30 nmol/L), and ACTH was again low (4 ng/L). With Cyclical Cushing's likely, weekly 24 hr UFC was measured and showed cycling from 42 nmol/24H to 6,147 nmol/24H over 4 weeks. ACTH cycled from 3 ng/L to 12 ng/L. During the inactive phase, the patient complained of severe fatigue suggesting transient secondary adrenal insufficiency.
Discussion
Central serous retinopathy is a known ophthalmological presentation of Cushing's. The diagnosis of cyclical Cushing's explains the variation in ACTH measurements at presentation. Cyclical Cushing's presents special challenges; if ACTH is low when cycling out of hypersecretion, ACTH-independent Cushing's may be mistakenly diagnosed, or IPSS may be misinterpreted to exclude an ectopic ACTH source (normal pituitary will have central-peripheral gradient). It will be necessary to repeat the IPSS when we know the Cushing's syndrome is active.

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P299

An Insulinoma presenting post bariatric surgery

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A 54-year old female presented with fluctuating consciousness and seizures 4-weeks after gastric sleeve surgery. On admission blood glucose was 1.1 mmol/l, GCS was 10 and she was tachycardic. Examination was otherwise unremarkable. Her GCS improved after Glucagon and Glucogel. She described episodes of disorientation, slurred speech, fatigue and dysthesia since her surgery. These occurred particularly in the morning and her symptoms improved after eating. Her fluctuating consciousness continued necessitating intubation. Blood glucose levels were poorly documented at this time. Cerebral imaging and lumbar puncture were normal but an EEG showed non-convulsive status epilepticus. Administration of Levetiracetam led to resolution of seizure activity. Over the following days she had recurrent hypoglycaemia, particularly in the early morning, which had no temporal relation to meals. Her gastric sleeve diet was therefore abandoned. During one episode of hypoglycaemia (2.7 mmol/L), Insulin and C-peptide were found to be inappropriately raised (36.3 mU/L and 2.08 nmol/L respectively; reference ranges $<$13.0 mU/L and 0.36-1.12 nmol/L), raising the likely diagnosis of insulinoma. MRI of pancreas demonstrated a 16 mm pancreatic head mass, however an Octreotide scan was negative. Interestingly, review of a CT scan from 2007 showed that a small pancreatic lesion had been present then. At a surgical MDT, Whipple's procedure, tumour enucleation and radiofrequency ablation were all considered but due to the patient's BMI (39) these were felt to be either too high-risk or too technically challenging. Good glycaemic control was achieved with Diazoxide (200 milligrams BD). The plan is to reassess the patient for curative surgery if she can loose weight. This unusual case raises the possibility that the insulinoma had contributed to her weight gain. Its presence was only revealed following gastric sleeve surgery and commencement of the post surgery diet. We will discuss this in more depth and review the causes of hypoglycaemia post bariatric surgery.

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P300

Diagnostic challenge of non-invasive and invasive imaging modalities for insulinoma

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Background
Neuroglycopenic symptoms in insulinoma could persist for years before localising the source of endogenous hyperinsulinaemia. 90% of insulinomas are sporadic, solitary and $<$ 2 cm in diameter, and can be associated with multiple endocrine neoplasia-1 (MEN-1). Insulinoma is an emerging clinical entity with a huge diagnostic challenge as tumour growth varies from months to years before tumour localisation.
Case Report
A 59-year old woman was referred with intermittent confusion, sweatiness, palpitations, and tremors. Her fasting glucose was 2.1 mmol/L on several occasions without visual changes and galactorrhoea. Thyroid function was normal. Cortisol was 372 nmol/L with raised C-peptide(1085 pmol/L) and failure of suppression of insulin (101 pmol/l). Self-monitored capillary glucose ranged from 2.0–4.3 mmol/L. Initial non-invasive imaging, including dual phase computed tomography (CT) abdomen and magnetic resonance (MR) imaging of pancreas proved unsuccessful at identifying any tumour. Annual monitoring of fasting gut hormones including insulin, C-peptide and chromogranin A remained consistent with hyperinsulinaemic hypoglycaemia. For 3 years, she adhered to regular meals containing complex carbohydrate, avoiding prolonged fasting with reasonable symptom control, and was reluctant to undergo further investigations. She wasn't able to tolerate a trial of diazoxide. Three years after initial imaging, symptoms became re-emerged uncontrollably. Repeat magnetic resonance imaging of pancreas and post-contrast octreotide scan performed, followed by intraoperative ultrasound. Despite lack of radiological confirmation from initial scans, successful intraoperative endoscopic ultrasound demonstrated 7$\times$6 mm hypoechoic lesion at tail of pancreas. A curative distal pancreatic resection proved vital with histological confirmation of insulinoma. Twenty-four months post-operatively, she remained well with complete resolution of symptoms and no further hypoglycaemia.
Conclusion
Absence of a tumour on serial non-invasive MR imaging modalities does not completely exclude the possibility of insulinoma. Further monitoring in cases of persistent hyperinsulinaemia may require a complete gut hormone profile and consideration of invasive imaging from experts in intraoperative ultrasound.

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P301

Pituitary tumours and bradycardia/complete heart block-an association or incidental findings?

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Introduction
Presentation of pituitary tumours can be variable.If is a functioning pituitary tumour the clinical manifestation will be that of excessive hormone secreted, and if is a non functioning pituitary tumour, the presentation will be that of target endocrine organ insufficiency.
Bradycardia/complete heart block may be a non specific presentation of non functioning pituitary tumours.
Cases
We present 2 cases presenting with non functining pituitary tumours and bradycardia.
1.54 years old man was admitted with left sided painless eye ptosis.He denied headaches.His ECG showed bradycardia 2:1 block.
He had CT head which revealed bulky pituitary followed by MRI which showed pituitary macroadenoma measuring 1.9 cm but no optic chiasma compression.His blood test revealed hypopitutarism as evidenced by secondary hypothyroidism FT4 8.9, FT3 3.4, normal TSH, secondary hypogonadism with low testosterone level of 7.9 and inappropriate normal LH 1.8 and FSH8.1.
His past medical history include hypertension, hypereosinophilic syndrome and gastritis.
2.85 years old man presented with collapsed with loss of consciousness. There was no evidence of head injury or seizures. He had no focal neurology.He complained of 4 months history of memory loss and general lethargy. He denied having headaches or visual disturbance. His past medical history included chronic back pain and hiatus hernia. On admission he was found hypotensive BP 108/60), bradycardic. Blood test revealed mild hyponatraemia, 9 am cortisol was 93, prolactin 533, testosterone 0.6, LH 0.4, FSH 2.4, TSH 1.13 and FT4 10. ECG revealed junctional bradycardia MRI scan of his brain revealed a large pituitary tumour ($1.2\times2.2\times1.5$)cm compressing the optic chiasm.
Discussion
Various central nervous diseases including pituitary tumours may be associated with arryhythmias including bradycardia. Secondary hypothyroidism may contribute to bradycardia and correcting the hypothyroidism with levothyroxine is important before consideration of permanent pace maker.
Conclusion
Pituitary tumours presenting with bradycardia is not uncommon as demonstrated by the above cases. Bradycardia may be due to secondary hypothyroidism or the effect on the autonomic nervous system.

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P302

Unaffected genetic testing in families at risk of phaeochromocytoma or paraganglioma

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75% of patients presenting with a phaeochromocytoma (PCC) or paraganglioma (PGL) have no relevant family history, but a germline pathogenic variant is identified in 30–40%. In our genetic endocrine clinic, over 80% of patients with malignant PCC or PGL have SDHA/SDHB/SDHC/SDHD/MAX or FH pathogenic variants identified, confirming high heritability in severe disease.
We describe a series of seven patients from five families concerned about their risk of developing PCC or PGL, as a parent had died from PCC or PGL and no genetic testing had been performed. One patient had a familial pattern of disease. Four had symptoms indicative of possible catecholamine excess. None had features of neurofibromatosis type 1. Baseline biochemical and radiological screening was performed and no abnormalities were detected. Routinely, genetic testing would only be offered if a diagnosis of PCC or PGL had been confirmed.
We obtained PCC or PGL tumour blocks from four of the deceased. Tumour DNA was extracted and partial genetic testing of SDHB and SDHD was successful in one case, but the tumour material was exhausted and no pathogenic variant was found. In three other cases, SDHB immunostaining on tumour tissue showed absent staining, indicating a possible SDHx pathogenic variant, however somatic tumour testing failed.
After careful discussion, unaffected or indirect testing was offered to each family, adopted from our experience in the genetics clinic of unaffected BRCA gene testing.
Three pathogenic variants were identified (2 SDHB, 1 SDHC), confirming an inherited susceptibility to PGL/PCC in three families.
Conclusion
Unaffected genetic testing in carefully selected cases may confirm a diagnosis, enabling timely surveillance and intervention in those with proven inherited PCC or PGL susceptibility. To reduce the need for unaffected testing, we recommend all patients with malignant PCC or PGL are offered genetic testing, as archival somatic tissue testing may not be informative.

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Nursing Practice

P311

The value of a holistic needs assessment tool in the care of patients with acromegaly

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Background
It is well established that patients with acromegaly have compromised quality of life both during active disease, as well as whilst on remission. (1). In the recent years, there has been increasing emphasis on the importance of considering health-related quality of life (QoL) outcomes in the care of patients with acromegaly. The University Hospitals Birmingham NHS Foundation Trust introduced and implemented the use of a holistic needs assessment (HNA) tool in the Pituitary Service in 2014.
Aims
To gain a better insight of the needs of patients with acromegaly, as reported by them in the HNA questionnaire.
Patients and Methods
A structured HNA, incorporating 11 indicators of psychosocial distress (issues concerning: original diagnosis and treatment; complications; hormone; heart problems; fertility; sexual; psychological; social/family; education/employment; healthy lifestyle, and spirituality/faith/belief) was offered to all patients with acromegaly on arrival at the Pituitary clinic prior to consultation with the health care professional. An audit of the responses was carried out over a 15-month period (May 2014 – August 2015).
Results
A total of 92 patients (with active disease or in remission following various treatments) completed a HNA form. Of the 11 areas assessed, patients were most concerned about their hormone issues (50% of patients indicated that they are either worried/very worried/extremely worried), complications of their condition and treatment (42.39%), original diagnosis and treatment (40.21%), healthy lifestyle (40.21%), and heart problems (36.96%). Additionally, more than quarter (28.26%) of patients expressed concerns about their psychological well-being.
Conclusions
The use of the HNA tool has enabled us to structure and adapt our consultation to focus on what matters most to each individual patient. It is proving to be a very reliable tool in identifying patients' needs as well as identifying the support that patients consider to be a priority.

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P312

Endocrine clinical nurse specialist nurse led clinics – Legal considerations of practice.

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Introduction
In 2015, a service evaluation of endocrine clinical nurse specialist (CNS) nurse led clinics (NLC) demonstrated they took on a variety of formats to meet local service and patient population requirements. Continuing professional development (CPD) is a fundamental and legal requirement of nursing practice. However, because of the introduction of NMC revalidation in 2016 and recent medicolegal developments such as confidentiality, duty of candour, consent and freedom to speak up (NMC, 2015, DOH, 2009) we sought to establish how this currently impacts on endocrine CNS NLC.
Method
An online questionnaire, consisting of 13 multiple choice and open-ended questions, was distributed to 119 nurse members of the Society for Endocrinology (SfE).
Questions focused on the legal framework and knowledge surrounding NLCs. We aimed to capture a larger cohort of clinics and assess developments within this important aspect of endocrine care.
Results
Preliminary findings demonstrated that 82.6% of endocrine CNS who responded currently run NLC, of which 95% worked autonomously. Clinical responsibility fell to the endocrine CNS, consultant in charge of the patients care or both. Informed consent was obtained for a variety of procedures, with dynamic function testing being the most frequently consented (94.1%). 70% personally took consent, while 22.2% relied on consent obtained by another healthcare professional (HCP). Consent was predominately verbal (76.9%), but only around half of CNSs were trained to obtain consent. Over half (65%) were independent non-medical prescribers with 43.5% undertaking relevant annual CPD. Complaints mainly involved communication issues. 66.7% of nurses audited their practice with 27.3% resulting in a change in practice.
Conclusions
There is disparity in the training and process of obtaining consent by endocrine CNS. Establishment of guidance would be useful and would address legal implications. CPD should form an integral part of the prescribing process and incorporation of audit should be standardised into endocrine CNS practice.

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P313

Audit Outcomes of a Nurse Led, Hyperthyroid Telephone Clinic (HTC)

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Introduction
The HTC in Nottingham was set up in 2013. Patients are referred to HTC from their first appointment with the Endocrinologist for regular follow up, as per national guidelines. Each Patient is reviewed by a Band 6 Nurse or Endocrine CNS, & counter-checked by an Endocrinologist in clinic.
There were two aims to this audit:
1. Assess patient satisfaction through a questionnaire (with an aim to capture 1/3 of HTC patients, if possible);
2. Assess clinical quality and effectiveness by reviewing clinical outcomes.
Methodology
Between May and September 2016, retrospective HTC patients were identified from their notes by Gateway staff and given an anonymous questionnaire to complete. The questionnaire was then given back to the Gateway staff and placed into an envelope. Each questionnaire had 17 questions and space for general comments.
May 2016 clinic lists were reviewed for patient outcomes, compliance and a cost analysis.
Results
Questionnaire:
N = 79/350 (23%);
An overall positive response was classed as >90%;
13/17 questions received a positive response over 90%;
100% said they would use HTC again;
May – October = 785 HTC patients, saving £14,718 in Consultant appointments;
Average follow up/patient = 12 weeks.
May 2016 HTC List Outcomes:
114 patients listed in 12 HTC sessions – 25% male, 75% female.
Interventions:
21% had anti-thyroid medication dose titrated;
4% were discharged to GP;
2% stopped their anti-thyroid treatment due to side effects;
1% had a drop in neutrophil count to 1.4 (2–7.5);
35% remained on the same dose of anti-thyroid medication.
27% failed to have bloods pre HTC.
Conclusions
Overall patient satisfaction of HTC is excellent; there was a high 'DNA' rate for blood tests before appointments; HTC is cheaper than a clinic appointment and an effective way to follow up thyroid patients regularly, within national guidelines.
Future Plans
Reduce slot time from 20 minutes to 15 minutes; CNS Nurse Prescriber to oversee each HTC follow up instead of Consultant; reduce 'DNA' rate (Text reminders?); repeat audit in 12 months.

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Annette Louise Seal Memorial Award

P314

UK experience with continuous subcutaneous hydrocortisone infusion in patients with adrenal insufficiency

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Continuous subcutaneous hydrocortisone infusion (CSHI) is a novo treatment for adrenal insufficieny. This treatment aim to mimic body circadian rhythm by providing a continuous slow infusion subcutanously.
We summarise our experience with 5 patients: 1 with primary adrenal insufficiency and 4 with secondary adrenal insufficiency. There are 1 male and 4 females with a mean age 31. All these patients were self referred and have tried various oral preparations with their local endocrinologists
A clinical protocol for CSHI was devised. Medtronic paradigm pump was loaded with Solu-Cortef hydrocortisone with each unit converting to each mg of hydrocortisone. Once commencing on CSHI cortisol series were taken during the day. AddiQoL scores were taken at baseline and at set intervals. Titration was based on symptoms, serum cortisol and 24 hours urinary cortisol.
Outcomes
Patients who were not doing well on oral steroid has poorest AddiQoL scores and gain most from the improvement in QOL scores. All 5 patients shown improvement in AddiQoL from baseline and continue to improve throughout the CSHI. Symptoms that were presence at baseline eventually subsided as we progress into the treatment. Infusion site infecton subside as the infusion rate was titrated downward based on the 24 hour urinary cortisol results. 1 patient who uses wheelchair and another who required walking stick for mobilisation eventual achieve independent on day to day activities without aid. 1 patient was able to reduce hospital admissions when started CSHI.
Conclusion
CSHI is a safe and cost effective treatment and can be used as option for patients with poor tolerance with oral steroids. More data is needed to look at the long term impact of this new treatment. More NHS centres need to provide this as an options for patients who have poor tolerance to convention steroid replacement.

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Obesity and Metabolism

P315

Advanced NAFLD is common in bariatric surgical patients, poorly staged by non-invasive NAFLD biomarkers and is associated with adverse outcome

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Introduction
Non-Alcoholic Fatty Liver Disease (NAFLD) is reported to be common in patients undergoing bariatric surgery, but the diagnostic accuracy of non-invasive NAFLD biomarkers to stage disease and track progress longitudinally has not been assessed.

Methods
274 patients undergoing bariatric surgery were included in the study. Intra-operative liver biopsies were taken from 163 patients and histologically graded using the NAFLD Activity Score and Kleiner classifications. Established non-invasive biomarkers were measured (Enhanced Liver Fibrosis (ELF), AST/ALT, APRI, BARD, Fib-4, NAFLD Fibrosis Score (NFS)) and ROC curve analysis was used to determine the utility of each test. Biomarkers and metabolic health markers (including HbA1c) were recorded prior to surgery (mean 17.2+/−20.3 days), 6 and 12 months post-operatively and compared using repeated measures ANOVA.
Results
Steatosis was present in 84.6%, advanced fibrosis in 23.1% and non-alcoholic steatohepatitis (NASH) in 11.9% of intra-operative biopsies. All biomarkers performed poorly in identifying advanced fibrosis (AUROC = 0.60-0.69). ELF best predicted cirrhosis (AUROC = 0.73), however NICE-recommended ELF cut-off thresholds failed to predict 94% of cases of advanced fibrosis and 80% of patients with cirrhosis.
There was rapid post-operative weight reduction with 67.7% excess weight loss 12 months post-operatively ($P = 0.00$). Metabolic health markers improved during the 12 month post-operative period (including HbA1c 6.2% to 5.3% $P = 0.00$, total cholesterol:HDL ratio 4.1 to 3.3 $P = 0.00$). In contrast, NAFLD biomarkers worsened (including AST/ALT 0.9 to 1.2 $P = 0.01$; Fib-4 1.0 to 1.1 $P = 0.03$).
With a minimum 1 year of post-operative follow-up ($n = 215$), hepatic decompensation incidence was 2.3%, occurring a median of 342 days post-operatively. Decompensated liver disease was associated with intra-operative biopsy-proven cirrhosis ($P = 0.01$).
Conclusion
Advanced NAFLD is common in bariatric surgical patients and intra-operative cirrhosis is associated with hepatic decompensation in the first post-operative year. Currently available non-invasive biomarkers poorly predict histological NAFLD severity and there is a disconnect between improvement in metabolic variables and non-invasive NAFLD assessments post-operatively. Improved biomarkers and an increased awareness of the prevalence of advanced NAFLD in patients undergoing bariatric surgery are required.

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P316

Low vitamin B12 in pregnancy is associated with adipose derived circulating miRNAs targeting PPARγ and insulin resistance

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Background
Low vitamin B12 (B12) during pregnancy is associated with higher maternal obesity, insulin resistance (IR) and gestational diabetes (GDM). However, it is not clear whether these are causally related.
Objective
B12 is a key co-factor of the DNA methylation cycle (1-carbon metabolism). We hypothesize that B12 plays a role in epigenetic regulation by altering circulating miRNAs (miRs) during adipocyte differentiation and results in an adverse metabolic phenotype.
Methods
Maternal venous blood samples ($n = 91$) and subcutaneous adipose tissue ($n = 42$) were collected at delivery. Human pre-adipocyte cells (Chub-S7) were differentiated in various B12 concentrations (1) Control: (B12 = 500nM); (2) LowB12 (B12 = 0.15nM) (3) NoB12: (B12 = 0nM). Serum B12, folate, lipids and plasma 1-carbon metabolites were determined. miR profiling, miR expression and gene expression were measured.
Results
We demonstrated that low B12 in human pregnancy was associated with higher BMI and in maternal adipose tissue, increased expression of adipogenic and lipogenic genes. Our *in vitro* human adipocyte model showed that adipocytes differentiated in B12 deficient conditions accumulated more lipids, had higher triglyceride levels and increased adipogenesis and lipogenesis. MiR array screening revealed differential expression of 133 miRs. We then validated 12 miRs related to adipocyte differentiation and function. MiRs targeting PPARγ (miR-27b, miR-23a, miR-130b), CEBPα (miR-31), adipocyte differentiation (miR-143, miR-145, miR-146a, miR-221, miR-222, miR-125b) and IR (miR-103a, miR-107) were altered in adipocytes and its secretion. *In vivo* validation in pregnant women with low B12 confirmed a similar pattern of altered miR expression in human adipose tissue and circulating miR expression in serum. After adjusting for likely confounders, multiple regression analysis revealed an independent association of B12 with BMI and was mediated by altered circulating miRs targeting PPARγ (miR-27b, miR-23a) and IR (miR-103a, miR-107).
Conclusions
Our study shows that low B12 levels in pregnancy alters adipose derived circulating miRs, which may mediate an adipogenic and insulin resistant phenotype leading to obesity.

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P317

The use of intestinal organoids to investigate nutrient sensing

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Intestinal nutrient sensing and transport are gaining increasing attention in the field of obesity research. To date, *in vitro* studies in this area have largely used two dimensional (2D) cell culture models. However, 2D cell cultures are limited by a lack of cellular heterogeneity, behaviour, and communication observed *in vivo*. There has consequently been growing interest for the application of three-dimensional (3D) cell culture systems. Recently, a 3D model system cultured from mouse intestinal crypts has been developed, known as mini-gut or organoid culture. Supplemented with the appropriate medium and growth factor cocktail and cultured in an extracellular matrix, stem cells derived from isolated mouse crypts are able to proliferate and differentiate into all cell types present in the *in vivo* intestinal epithelium. Crypts can be isolated from the different intestinal sections (duodenum, jejunum, ileum and colon) and grown up into organoids characteristic of the specific intestinal segment, enabling comparison studies between regions. These organoids functionally recapitulate intestine physiology, and are therefore a powerful model to investigate nutrient sensing and transport and subsequent incretin hormone secretion including intracellular signalling processes.
We have used intestinal organoids to investigate the role of specific nutrient sensing systems on gut hormone release. For example, hormone secretion assays in mouse ileum organoids have revealed significantly higher release of the anorectic gut hormone glucagon-like peptide-1 (GLP-1) after 24 hours of treatment with the amino acid L-Phenylalanine. This effect was significantly attenuated with the addition of a calcium-sensing receptor (CaSR) antagonist. This suggests that L-Phenylalanine stimulates GLP-1 release, and that the CaSR, a promiscuous amino acid sensor, may mediate satiety in the gastrointestinal tract via detection of amino acid products from protein digestion. This effect was recapitulated *in vivo*, suggesting that intestinal organoids are a useful tool for understanding physiological gut sensing mechanisms.

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P318

5β-reductase (AKR1D1) is a potent regulator of carbohydrate and lipid metabolism and inflammation in human liver

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Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of metabolic disease. Steroid hormones and bile acids are established regulators of metabolic phenotype. 5β-reductase (AKR1D1) is highly expressed in human liver where it inactivates steroid hormones and catalyzes a fundamental step in bile acid synthesis. We hypothesized that AKR1D1 plays a key role in hepatic metabolic homeostasis. Genetic manipulation of *AKR1D1* was performed in human liver HepG2 and Huh7 cells. Gene expression changes were confirmed by qPCR, glucocorticoid clearance and 5β-metabolites generation, using gas chromatography-mass spectrometry. *AKR1D1* over-expression decreased glucocorticoid receptor activation, as measured by luciferase reporter assays. RNAseq analysis in *AKR1D1* knocked down HepG2 cells identified dysregulated pathways impacting upon metabolic pathways, insulin action and fatty acid metabolism.

AKR1D1 knockdown increased glucose transporter mRNA expression and decreased cell media glucose concentrations, while increased intracellular glycogen levels. *AKR1D1* knockdown increased *FAS*, *SCD1*, *SREBP-1c* and *ACC1* expression, the rate-limiting step in *de novo* lipogenesis (DNL), and intracellular triglyceride, while cell media 3-hydroxybutyrate levels were reduced, indicative of impaired fatty acid oxidation. Mass spectrometry analysis of lipid composition demonstrated increased palmitic and palmitoleic acid production, consistent with increased DNL and fatty acid saturation. Furthermore, bile acid composition was altered with significantly increased chenodeoxycholic acid levels. Conversely, pharmacological manipulation of the bile acid receptors FXR and LXR using GW4064 (FXR agonist) and 22(S)-Hydroxycholesterol (LXR antagonist) rescued HepG2 cells from metabolic dysfunction by reducing lipogenic gene expression. *AKR1D1* knockdown increased proinflammatory cytokine IL-1β, IL-6 and IL-8 mRNA expression; changes were confirmed by elevated cell media IL-6 and IL-8 levels, increased IκBα degradation and induced IRE1α protein expression, indicative of inflammation and ER stress. In conclusion, AKR1D1 activity regulates steroid hormone and bile acid availability, potently modulating hepatic carbohydrate and lipid metabolism, in addition to an inflammatory phenotype, suggesting a crucial role in NAFLD pathophysiology.

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P319

The adverse metabolic phenotype associated with obstructive sleep apnoea is not driven by activation of the hypothalamo-pituitary-adrenal axis

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Glucocorticoid (GC) excess drives obesity, insulin resistance and type 2 diabetes. Obstructive sleep apnoea (OSA) is a prevalent condition associated with both activation of the hypothalamic-pituitary-adrenal (HPA) axis and an adverse metabolic phenotype. However, a causal link between these two features has not been established. We designed a novel human model of intermittent hypoxia (IH) aimed at replicating the systemic insulin resistance associated with OSA to determine whether limiting GC availability has a beneficial metabolic effect.
Healthy male participants ($n=17$, age: 25 ± 6 yrs; BMI:24.1 ± 1.7 kg/m^2) underwent a hyperinsulinaemic-euglycaemic clamp incorporating stable isotopes with adipose tissue microdialysis and biopsy, under conditions of normoxia. Volunteers were then randomized to receive either the GC receptor antagonist, RU486 (600 mg od, 1 week) or no treatment. All investigations were then repeated under conditions of IH. IH was achieved by alternating the FiO_2 of inspired gases between air (FiO_2 21%) and a hypoxic gas mix (FiO_2 5%; balance nitrogen) to achieve 12 desaturations/hr.
In the fasted-state under normoxia, RU486 improved adipose tissue insulin sensitivity (significant reductions circulating non-esterified fatty acids (NEFA), glycerol and Adipo-IR all $P<0.05$). Our model of IH successfully replicated features of OSA ($11.4+/-0.8$ desaturation/hr. $87+/-4$ $\%O_2$ saturations). IH induced insulin resistance as measured by reduced insulin-mediated suppression of circulating triglyceride (TAG) and VLDL TAG ($P<0.05$). In the fed, hyperinsulinaemic-state, and under IH, RU486 worsened the adverse metabolic features (reduced insulin-mediated suppression of TAG; VLDL-TAG; βOH-Butyrate, all $P<0.05$). These data endorse our previous observations demonstrating that GCs enhance insulin action *in vitro* and *in vivo* in the fed-state. In conclusion, we have demonstrated a differential effect of GC receptor antagonism in the fed and fasted-state. Limiting GC action under conditions of IH worsened insulin resistance suggesting that activation of the HPA axis in OSA does not drive the development of an adverse metabolic phenotype.

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P320

Androgen excess is highly prevalent in women with idiopathic intracranial hypertension and is biochemically distinct from polycystic ovary syndromes

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Idiopathic intracranial hypertension (IIH) is a condition of unknown aetiology characterised by raised intracranial pressure, chronic headaches and blindness. Akin to polycystic ovary syndrome (PCOS), IIH patients are almost exclusively obese females of reproductive age. A distinct androgen excess profile has been noted in PCOS. Here, we aimed to delineate androgen metabolism in IIH compared to PCOS and simple obesity.
Women with IIH ($n=70$), alongside age- and BMI-matched cohorts with PCOS ($n=60$) and simple obesity ($n=40$), were recruited. Comprehensive serum androgen profiling, including 11-oxygenated androgens recently shown to represent the major androgens in PCOS, was carried out by by liquid chromatography-tandem mass spectrometry (LC-MS/MS) and 24-h urine steroid profiling by gas chromatography-mass spectrometry in all three groups. In IIH women ($n=49$) and a female cohort with non-IIH neurological disease ($n=30$), we also quantified androgens in cerebrospinal fluid (CSF) utilising LC-MS/MS.
PCOS patients had increased insulin resistance, as measured by HOMA-IR ($P<0.05$), while HOMA-IR in IIH did not differ from controls. Serum testosterone was higher in IIH compared to both PCOS and control women ($P<0.001$ for both); conversely, serum androstenedione was higher in PCOS women than in IIH ($P<0.001$) and controls ($P<0.01$). Serum levels of the 11-oxygenated androgen precursors 11β-hydroxyandrostenedione and 11-ketoandrostenedione were increased in PCOS ($P<0.0001$), while levels in IIH patients did not differ from controls. Systemic 5α-reductase activity, as measured by the ratio of 5α-tetrahydrocortisol/tetrahydrocortisol, was higher in IIH women compared to both PCOS and controls ($P<0.05$ for both). IIH women had significantly increased CSF androstenedione and testosterone compared to controls (all $P<0.0001$).
We show that women with IIH have a distinct androgen excess phenotype compared to PCOS and simple obesity, with higher active serum androgens, 5α-reductase activity and increased CSF androgens. Further studies are needed to understand the mechanistic role of androgen excess in the pathogenesis of IIH.

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P321

Rectal and oral administration of L-Phenylalanine supresses food intake and modulates neuronal activation in appetite-regulating brain regions in rodents

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High protein diets are highly satiating but hard to maintain. By understanding the mechanisms underlying these effects we may be able to identify new anti-obesity therapies. Protein is broken-down into amino acids in the gut which are detected by a series of nutrient sensors. The calcium sensing receptor (CaSR) is primarily activated by calcium ions, but is positively allosterically modulated by aromatic amino acids, especially L-phenylalanine. Stimulation of the CaSR by L-phenylalanine can stimulate glucagon-like peptide-1 (GLP-1) secretion, but its role in the secretion of other gut hormones is unclear.
Studies in our department have shown that oral administration of L-phenylalanine suppresses food intake in rodents. We therefore aimed to investigate the mechanisms underlying these effects and which region of the gut is involved.
We examined the effect of orally and rectally administered L-phenylalanine on food intake and neuronal activation in mice. To investigate whether L-phenylalanine might be being systemically absorbed to have a direct effect on neuronal activation, we also investigated CaSR expression in the brain regions activated in response to L-phenylalanine.
In vivo, oral and rectal administration of L-phenylalanine reduced food intake and increased neuronal activation in the area postrema of mice. Immunohistological staining showed that the CaSR is expressed in the area postrema of mice. Mice orally administered L-phenylalanine also had significantly lower gastric inhibitory peptide (GIP) plasma levels.
Previous work suggests that oral L-phenylalanine can increase GLP-1 secretion and improve glucose tolerance, so the inhibitory effect of L-phenylalanine on GIP was unexpected. Further work is required to determine the role of the CaSR and L-phenylalanine in glucose homeostasis. In addition, the role of central nervous system amino acid sensing via the CaSR in the anorectic effects of L-phenylalanine requires further investigation.

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P322

Cholestatic pregnancy alters the gut incretin response to diet, affecting GLP-1, PYY and FGF19 secretion, with reversal of changes associated with ursodeoxycholic acid treatment

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Introduction
Intrahepatic cholestasis of pregnancy (ICP) is characterised by maternal pruritus and raised serum bile acids, and is associated with adverse fetal outcomes (e.g. preterm birth, neonatal unit admission and stillbirth). Maternal metabolic impacts include higher rates of gestational diabetes mellitus, hypertriglyceridaemia and hypercholesterolaemia. Glucose and lipid metabolism are influenced by gut incretin release, and bile acids are commonly ligands for receptors whose activation results in these hormones being released. We sought to assess the effects of pregnancy and cholestasis upon lipid, glucose and incretin levels, and whether these can be reversed by treatment with ursodeoxycholic acid (UDCA), the most commonly-used treatment for ICP.
Methods
100 women were given a standardised diet for 24 hours, during which serial blood sampling was performed at 9 timepoints. Participants were pregnant women with ICP or non-pregnant women with a history of ICP, with matched controls for each group. Bile acids, lipids, glucose, GLP-1, PYY, FGF19 and C4 were measured, and results compared using multiple measures of ANOVA and student's T tests.
Results
The gestational increases in serum triglycerides, total and LDL cholesterol were exacerbated by ICP. The GLP-1 response to a meal was lower for women with ICP, and was improved with UDCA treatment. Basal PYY was higher for women with ICP, and peaked at a higher level post prandially than for women with normal pregnancies, or non-pregnant controls. Normal pregnancy resulted in lower peak serum FGF19; this was unchanged in non-UDCA treated ICP, but serum concentrations increased with UDCA treatment. UDCA treatment also caused increased faecal lithocholic acid concentrations.
Conclusions
The metabolic disturbances of ICP are contributed to by altered intestinal responses to food. These can be ameliorated by treatment with UDCA, a new indication for the drug in treatment of ICP.

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P323

A randomised controlled trial of vitamin D treatment on markers of liver fibrosis in obese women with Polycystic Ovary Syndrome

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Context
Polycystic ovary syndrome (PCOS) has been linked to non-alcoholic fatty liver disease (NAFLD) that carries an increased risk of liver cirrhosis. The Enhanced Liver Fibrosis (ELF) score comprises serum hyaluronic acid (HA), procollagen III N-terminal peptide (PIIINP) and tissue inhibitor of metalloproteinase-1 (TIMP1) that correlate with hepatic fibrosis staging.
Objective
To determine the effect of vitamin D supplementation on liver fibrosis markers.
Design
A randomized, double-blind, placebo-controlled study.
Setting
A tertiary care setting in the UK.
Participants
Forty obese women with PCOS.
Intervention
Randomization to either vitamin D 3200 IU daily or placebo for 3 months.
Main outcome measures
The primary outcome was ELF score change, with alanine aminotransferase (ALT), hormonal, metabolic and cardiovascular risk marker changes as secondary outcomes.
Results
Vitamin D supplementation showed an ELF score reduction compared to placebo ($-7.6\pm9.6\%$ vs. 0.4 ± 8.9; $P=0.02$) with a corresponding decrease in the component fibrosis markers; HA ($-31.2\pm31.9\%$ vs 16.9 ± 57.1; $P<0.01$) and PIIINP ($-18.6\pm20.4\%$ vs 8.0 ± 27.2; $P<0.01$), and a fall in ALT with vitamin D treatment ($-16.7\pm25.7\%$ vs 21.9 ± 28.3; $P<0.01$). Within group analysis revealed vitamin D alone showed ELF score reduction ($P<0.01$) with a reduction in HA ($P<0.01$), PIIINP ($P<0.01$) and TIMP-1 ($P<0.05$). There were no changes in the hormonal, metabolic or cardiovascular risk profiles between groups.
Conclusion
Vitamin D supplementation improved hepatic fibrosis markers (HA, PIIINP, TIMP-1) in obese women with PCOS with a reduction in the ELF score.

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P324

Leptin receptors localise to β-cells in the fetal ovine pancreas, but do not appear to influence β-cell mass *in utero*

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Babies born to mothers with diabetes during pregnancy are exposed to high circulating leptin before birth and, in turn, are at increased risk of developing diabetes in later life. In pancreatic islets isolated from fetal sheep, leptin influences β-cell proliferation in a bimodal manner. This study examined the effect of exogenous leptin infusion and leptin receptor antagonism on pancreatic β-cell mass in the sheep fetus *in vivo*.
All procedures were performed under the UK Animals (Scientific Procedures) Act 1986. In 28 pregnant ewes at 118-120 days of gestation (d; term ~145d), the femoral artery and vein of the fetus was catheterized under general anaesthesia. For 5 days from 125d, fetuses were infused i.v with either saline (2 ml/day, 0.9% NaCl, $n=13$), recombinant ovine leptin (LEP1, 0.6 mg/kg/day, $n=8$ or LEP2, 1.4 mg/kg/day, $n=7$) or recombinant ovine long-form leptin receptor antagonist (LRA, 4.6 mg/kg/day, $n=5$). Arterial blood was collected before and during treatment. After maternal and fetal euthanasia, the fetal pancreas was weighed and examined for leptin receptor expression and β-cell mass using immunohistochemistry and stereological point counting. Data were analysed by two-way ANOVA.
Leptin receptor protein was localised to the β-cells of the fetal ovine pancreas at 130d of gestation. Plasma concentrations of leptin were increased on all days of infusion in LEP1 and LEP2-treated fetuses ($P<0.05$). Neither leptin nor LRA infusion influenced fetal body weight, absolute or relative measurements of pancreas or β-cell mass.
The expression of leptin receptors in pancreatic β-cells of the sheep fetus indicates a role for leptin in islet development before birth. In this preliminary study, however, pancreatic β-cell mass was not affected by exogenous leptin infusion or antagonism of the long-form leptin receptor. Further investigation is required to assess whether leptin regulates pancreatic development and secretory function *in utero* with consequences for the offspring of diabetic pregnancies.

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P325

Evaluating the role of testosterone in cerebrospinal fluid secretion

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Idiopathic intracranial hypertension (IIH) is a condition characterised by raised intracranial pressure (ICP) that primarily affects obese women of reproductive age. The aetiology is poorly understood but involves imbalance of cerebrospinal fluid (CSF) secretion and absorption. IIH patients share similar phenotypic characteristics to PCOS patients, a condition with a distinct androgen signature. We hypothesise that obesity and androgen excess maybe pathogenic in IIH through dysregulation of CSF secretion and hence ICP.

In this study we aimed to develop an *in vitro* CSF secretion assay and then evaluate the impact of testosterone on CSF secretion. An immortalised rat choroid plexus epithelial cell line (Z310 cells) was infected with an adenoviral vector containing the ATP:ADP ratio sensor Perceval. Na^+/K^+ ATPase activity is the rate limiting step in CSF secretion and a validated surrogate for CSF secretion. Na^+/K^+ ATPase activity was determined following acute administration of the specific inhibitor ouabain (1 mM), the change in ATP:ADP ratio indicated Na^+/K^+ ATPase activity. The assay was validated and additionally challenged with acetazolamide (1 mM, 2 days), a drug used clinically to reduce CSF secretion. Acetazolamide reduced the ATP:ADP ratio (indicating a reduction in CSF secretion) ($P<0.05$) compared to control. Ultimately, Z310 cells were incubated with testosterone (100 nM, 2 days) and the ATP:ADP ratio was noted to be increased ($P<0.0001$) compared to vehicle, indicating increased Na^+/K^+ ATPase activity and hence increased CSF secretion. Furthermore real-time quantitative PCR demonstrated increased expression of carbonic anhydrase II and III ($P<0.05$), key components in generating the ion gradients required for CSF secretion.

We have developed a novel *in vitro* CSF secretion assay though quantification of Na^+/K^+ ATPase activity. Testosterone increased Na^+/K^+ ATPase activity, indicating increased CSF secretion. We speculate that testosterone may have a pathogenic role in IIH through modulation of CSF formation and increasing ICP.

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P326

Low vitamin B12 induces *de novo* lipogenesis in human hepatocytes

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Background

Vitamin B12 (B12) deficiency results in disturbance of 1-carbon metabolites [methylmalonyl coenzyme A (MMA), homocysteine and S-adenosyl homocysteine (SAH), S-adenosyl methionine (SAM) and methionine] that collectively affect lipogenesis leading to risk of cardiovascular diseases. In clinical studies, B12 deficiency is associated with higher BMI and dyslipidaemia (high triglycerides and low HDL). The role of B12 in hepatic metabolism of lipids in humans is unexplored. Therefore, we investigated whether B12 deficiency affect hepatic *de novo* lipogenesis.

Methods

Human HepG2 cell line was cultured using custom made B12 deficient Eagle's Minimal Essential Medium (EMEM) and seeded in four different concentrations of B12 media such as 500nM (control), 1000pM, 100pM and 25pM (low) B12. Oil Red O (ORO) staining, RT-qPCR, total intracellular triglyceride (TG) assay and *de novo* TG biosynthesis using radioactive flux assay were employed to examine the effect of B12 on lipogenesis

Results

Hepatocytes in low B12 (25pM) had more lipid droplets compared with control (500 nM). Total intracellular TG levels were higher in low B12 hepatocytes. Gene expressions of nuclear transcription factors sterol regulatory element binding protein (SREBF1) and low density lipoprotein receptor (LDLR) were higher in low B12 conditions than control. Similarly, the gene expressions of the enzymes involved in *de novo* fatty acid synthesis [ATP citrate lyase (ACLY), Acetyl CoA carboxylase (ACC), fatty acid synthase (FASN) and elongation-of very-long-chain fatty acid (ELOVL6)], cholesterol biosynthesis [3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), 3-hydroxy-3-methylglutaryl-CoA synthase 1 (HMCS1), Isopentenyl-Diphosphate delta Isomerase 1 (IDL1)] and TG biosynthesis [stearoyl CoA desaturase (SCD), glycerol-3-phosphate acyltransferase (GPAT), acylglycerol-3-phosphate acyltransferase (AGPAT), phosphatidic acid phosphatase-1 (Lipin1) and diacylglycerol acyl transferase 2 (DGAT2)] were upregulated in low B12 conditions. Cellular uptake of radiolabelled fatty acid (^{14}C-oleate) for *de novo* TG biosynthesis assessed by scintillation was about 80% higher in low B12 hepatocytes.

Conclusion

Our data provide novel evidence that B12 deficiency dysregulates lipid metabolism in hepatocytes.

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P327

Male sexual dysfunction and hypogonadism improves following bariatric surgery

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Background

Male sexual dysfunction is common in obesity with complex underlying mechanisms. Testosterone replacement has often been initiated in clinical practice in the presence of sexual dysfunction and male obesity-associated secondary hypogonadism. The benefits to sexual functioning, however, are not well documented. The aims of the study were to investigate the relationship between sexual function and hypogonadism in severe obesity and to understand the impact of bariatric surgery (BS)-induced weight loss.

Methods

Sexual function was assessed using the European Male Ageing Study-Sexual Function Questionnaire in 26 men (mean age 49.4 ± 9.8, mean body mass index (BMI) 47.6 ± 7.0) before and in 14 of them (mean BMI 33.2 ± 5.3) reassessed between 6 to 12 months after BS. Participants were divided into two groups (low and high) based on the median values of the overall sexual function (OSF) domain of the questionnaire. Fasting morning blood samples were obtained for androgen profile.

Results

Erectile dysfunction was present in 73% of men before surgery. Fifty seven percent of men had a testosterone level of less than 9.5 nmol/l. Testosterone levels, however, were not significantly different between men with low (median 8.4) and high (median 9.4) OSF scores ($P=0.598$). OSF ($P=0.003$) and other domains of sexual function including erectile function ($P=0.04$) and sexual function-related distress ($P=0.004$) improved after BS. Serum testosterone increased ($P=0.003$) from median 9.4 nmol/l at baseline to (6.5–12.1) to 16.1 nmol/l (11.6–17.3) after BS. Similarly, sex hormone-binding globulin improved ($P=0.002$) from median 31.8 nmol/l (21.6–39.3) to 50.2 nmol/l (38.8–68.2). Changes in sexual function scores before and after BS did not correlate with changes in serum testosterone.

Discussion

Male sexual function improves after BS though this appears to be independent of changes in testosterone. Other factors like nerve and vascular function may have a more significant role. For symptoms of sexual dysfunction alone in the context of severe obesity, testosterone replacement may not be beneficial.

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P328

DNA methylation differs between lean and obese placenta and is influenced by maternal environment and fetal sex

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Obesity in pregnancy is associated with an increased risk of complications for mother and child. Epigenetic modifications have been proposed as an important underlying mechanism. As the placenta plays a key role in fetal nutrition and metabolism we hypothesized there would be placental DNA methylation differences between lean and obese placenta. DNA methylation array (Human Methylation 450K) was performed on placentas from $n=31$ obese (BMI > 40 kg/m^2) and $n=29$ lean (BMI < 25 kg/m^2) women. MiR-411 and *FABP1*, with false discovery rate (FDR) adjusted $P<0.05$, were selected for validation of DNA methylation differences by Pyrosequencing and measurement of mRNA levels by RT-qPCR. The mean (SD) percentage DNA methylation at miR-411 and FABP1 was significantly higher in obese placenta vs lean (68.9 (13.4)% vs 58.9 (15.8)%, $P=0.01$ and 89.7(2.76)% vs 85.8(7.16)%, $P=0.01$, respectively). MiR-411 DNA methylation was significantly higher in placenta from non-smoking obese vs non-smoking lean (70.42(9.6)% vs 58.63(17.4)%, $P=0.02$) women. MiR-411 DNA methylation percentage was highest in placentas from male babies born to obese mothers. There were no correlations between methylation levels and mRNA levels of miR-411 in either obese or lean placentas (miR-411 obese $r=0.21$,

$P=0.32$; lean $r=-0.32$, $P=0.14$). MiR-411 mRNA levels were significantly higher in current smokers vs non-smokers and ex-smokers (3.61(3.2) vs 1.3(1.2) vs 1.13(0.7), $P\leq0.05$). Infant BMI was positively correlated with mRNA levels of miR-411 in the lean but not obese group (lean $r=0.636$, $P=0.003$; obese $r=0.021$, $P=0.931$). In conclusion, DNA methylation and gene expression differ between lean and obese placenta, but are also influenced by maternal environment, fetal sex and infant BMI. The explanation for the lack of association of DNA methylation changes and gene expression changes is not known but may be due to the small magnitude of the DNA methylation changes. Further studies are needed to understand the functional outcomes of these DNA methylation changes.

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P329

Vitamin B12 deficiency triggers adipocyte dysfunction by enhancing triglyceride biosynthesis and pro-inflammatory cytokine production: a new agonist in metabolic disease?

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Background
Vitamin B12 (B12) is an essential micronutrient required for optimal hematopoietic, neurologic and other several metabolic reactions. Longitudinal studies and animal models showed that low maternal vitamin B12 deficiency is associated with the maternal obesity, development of insulin resistance and metabolic syndrome phenotype. Although the mechanisms underpinning metabolic disorders remain poorly defined, it has become increasingly clear that dysregulation of lipids and metabolic inflammation is associated with obesity and its comorbidities. Therefore, the aim of this study is to investigate the role of B12 in lipid regulation and inflammation in human adipocytes.
Methods
Human pre-adipocytes cell line (Chub-S7) and human primary pre-adipocytes were grown to confluence (day 0), differentiated in differentiation media for one week and maintained in nutrition media for next7 days (day 14). In order to analyse B12 deficiency effects, customized media with different concentrations of B12(25pM, 100pM, 1nM, 500nM) were used. On day 14,the condition media were collected and the cells were harvested for RNA and protein analysis, and stored at −80C until use. Gene expression was performed by q-RTPCR and cytokine secretion was determined by ELISA. Cellular triglycerides (TG) synthesis was quantified using radioactive tracing technique by incorporation of ^{14}C-oleate.
Results
Adipocytescultured in low vitamin B12 conditions showed significantly increased expression of genes involved in triglyceride synthesis such as Elongation Of Very Long Chain Fatty Acids Protein 6 (ELOLV6), Stearoyl-CoADesaturase(SCD), Glycerol-3-phosphateacyltransferases (GPAT), acylglycerolphosphateacyltransferase (AGPAT), phosphatidate phosphatase (LIPIN1), Diacylglycerol O-Acyltransferase 2 (DGAT2) and in lipid trafficking Fatty acid binding protein (FABP4). Cellular uptake of radio-labelled fatty acid (^{14}C-oleate) for *de novo* TG biosynthesis assessed by scintillation was significantly higher in low B12 condition. In addition, we also observed that the gene expression of pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-18 (IL-18), transforming growth factor beta (TGF-β),monocyte chemoattractant protein-1 (MCP-1/CCL2) and IL1-beta secretion were significantly increased in low B12 conditions.

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P330

Blunt response to a stress test and higher prevalence of risk polymorphism of glucocorticoid receptor gene (*NC3C1*) in obese patients

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Chronically exposure to stress promotes in individuals high intake of foods with high content of carbohydrates and fat and may develop obesity. Stress-induced sustained elevation of glucocorticoid serum levels may be due to impaired functioning of the hypothalamic glucocorticoid receptor GR, altering the hypothalamic-pituitary-adrenal axis regulation. As a result, chronically stressed individuals are unable to respond with higher cortisol levels when subjected to a new acute challenge. We hypothesized that obese patients that were exposed to chronic stress and classified as food-addicted will carry a risk polymorphism of *NR3C1* gene (GR) and a blunted saliva cortisol concentration after taking a stress test. Our aim was the identification of a risk biomarker to develop food addiction and obesity by combined effects of genetic factors and chronic stress in patients attending Dietetics and Nutrition Clinic of Security Services for State Workers in Mexico City.
Two-generation Mexican patients ($n=400$) participated in a transversal study (approved by the Ethical committee of the National Institute of Psychiatry RFM), signing the informed agreement. Men and women between 18 and 49 years old had their body mass index (BMI) registered. Menopause, smoking and alcohol drinking were exclusion criteria. Participants answered Yale's food addiction scale and a three-day food intake reminder. Before and after taking the Trier stress test, a sample of saliva was obtained and a previous sample of blood to evaluate cortisol levels and *NR3C1* polymorphism presence.
Results showed higher prevalence of food addiction in obese patients (44%) than controls (31%); food-addiction was more prevalent in women (38%) than in men (25.5%); cortisol levels increased after stress test (170 ± 71 vs. before $=46\pm8$ ng/mL) in patients with normal BMI but not in those with obesity (62 ± 22 ng/mL vs. before $=59\pm20$ ng/mL); women with food-addiction had higher ratio of risk polymorphism AG-GG/AA of *NC3C1* gene (0.56) than men or patients with no food addiction (0.34). Supported by CONACyT 233918 (FOSSIS)

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P331

Alterations in concentration and characteristics of circulating extracellular vesicles in morbid obesity

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Introduction
Obesity is associated with increased cardiovascular disease (CVD) risk but the underlying pathways are unclear. Extracellular vesicles (EVs) are circulating submicron particles containing proteins, enzymes and mRNA of their donor cells. They could mediate some of these risks by paracrine actions in target cells.
Aims
To compare the concentration and characteristics of circulating EVs from healthy volunteers (HV) and morbidly overweight (MO) patients.
Methods
EVs were isolated from venous blood in HV ($n=49$, age 33 ± 9 years, BMI 27 ± 6 kg/m^2) and MO ($n=21$, age 51.7 ± 11 years, BMI 55 ± 7 kg/m^2) subjects by ultracentrifugation. EV concentration and size distribution was established by Nanoparticle Tracking Analysis (NTA). Time Resolved Fluorescence (TRF) immunoassay was applied to establish cellular origin and adipokine content: CD41 (platelets), CD11b (monocytes/macrophages), CD235a (erythrocytes), CD144 (endothelial cells), CD9 (exosomes), TNFα, interferon γ, Fatty Acid Binding Protein 4 (FABP4) and PPARγ.
Results
EV concentration was significantly higher in the MO cohort ($13.8\pm3.1\text{x}10^{11}$/mL of plasma vs $4.6\pm0.4\text{x}10^{11}$/mL ($P<0.0001$)) but EV size distribution was similar, and predominantly in the exosomal range. CD9 and CD11b expression was not different between groups (50874 (17393-117688) vs 33222 (5536-104080); 14903 (2111-482013) vs 2756 2(404.0-112260) arbitrary TRF units (a.u.), respectively but expression of CD41, CD144 and CD235a was higher in the MO group: 22926 (10402-72078) vs 12962 (2568-34360); 12080 (3941-58123) vs 6076 (320.0-36106); 9585 (2668-24785) vs 5232 (416.0-25128) a.u., all $P<0.01$). EVs in MO subjects showed significantly higher expression of TNFα, interferon γ and FABP4 (27769 (15835-107710) vs 5425 (42.00-35230); 57028 (4558-157275) vs 37982(1240-103628); 38849 (11637-77248) vs 14445 (258.0-57026) a.u., all $P<0.001$) but no differences were seen in PPARγ expression.
Conclusions
Circulating EVs are elevated in morbidly obese subjects and are associated with enhanced platelet, endothelial and erythrocyte cell-of-origin expression. Coupled

with increased expression of FABP4, TNFα and interferon γ, this suggests that EVs may, at least in part, contribute to the increased CVD morbidity observed in obesity.

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P332

Reverse cholesterol transport and other functions of high density lipoprotein are enhanced after bariatric surgery

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Background
Emerging evidence suggests that impaired high density lipoprotein (HDL) function is associated with cardiovascular disease (CVD). HDL is essential for removing excess circulating cholesterol by reverse cholesterol transport (RCT). Additionally HDL reduces inflammation and oxidative stress, especially through paraoxonase-1. Whereas HDL's capacity to accept cholesterol from peripheral cells is key (i.e. cholesterol efflux capacity (CEC)), successful RCT depends on the transporters ATP-binding-cassette (ABC-) A1, G1 and scavenger receptor-B1 (SR-B1). Previous studies suggest weight-independent reductions in CVD after bariatric surgery (BS) although the exact mechanisms are unclear. We studied the impact of BS on HDL function with a specific focus on the principal components of RCT (CEC and transporters).
Methods
Markers of inflammation (Tumour Necrosis Factor- α (TNF-α); C-reactive protein (CRP)), oxidative stress (myeloperoxidase mass and paraoxonase-1 activity) and CEC *in vitro* were measured from 37 patients before, 6 and 12 months after BS. 12 participants had targeted gene expression (real-time quantitative PCR) of ABCA1, ABCG1, SR-B1 and TNF-α in gluteal subcutaneous adipose tissue biopsy samples. Results shown represent medians (interquartile range).
Results
HDL-C levels increased significantly 12 months after BS (1.18 mmol/l (1.00–1.33) at baseline to 1.4 mmol/l (1.2–1.7); $P<0.0001$). CRP, CETP and myeloperoxidase mass decreased with enhancements in CEC (Table). Serum TNF-α levels reduced from 14.5 pg/ml (1.5–58) to 2.3 pg/ml (0–51.8) to being undetectable (0–3 pg/ml) at 6 and 12 months post-surgery respectively ($P<0.0001$). Changes in HDL-C correlated significantly with changes in CRP ($r=-0.37$; $P<0.05$) and paraoxonase-1 ($r=0.43$; $P<0.05$). Gene expression of ABCA1 (*fold-change* 1.34; $P=0.05$) and ABCG1(*fold-change* 2.24; $P=0.005$) were augmented whereas TNF-α expression decreased non-significantly (*fold-change* 0.44; $P=0.57$). SR-B1 expression did not change (*fold-change* 1.12; $P=0.6$).
Conclusion
HDL function improves post-operatively with augmentation of RCT potentially contributing to reduction in CVD after BS.

Table 1 Changes in parameters at time-points.

Test	Median Baseline	Median 6 months	Median 12 months
CEC (%)	11.5 (10.5–14.6)	12.9 (9.7–15.2)	14.4 ¥* (13–18.4)
Myeloperoxidase mass (ng/ml)	973.1 (519.9–1460.8)	988.4 (515.8–1389.4)	756.0 ¥* (211.5–1162.6)
Cholesterol-Ester Transfer Protein Activity (nmol/ml/hr)	31.4 (13.6)	24.6 ᵀ (12.9)	27.0¥ (11.7)
Paraoxonase-1 Activity (nmol/ml/min)	77 (57–175)	83 (57–169)	87* (59–211)
CRP (mg/l)	6.52 (4.5–11.1)	3.2ᵀ (1.3–5.3)	1.1¥* (0.5–3.0)

Symbols denote $P<0.005$: ¥*12 v baseline*; **12 v 6*; ᵀ*6 v baseline*

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P333

Genes involved in zinc homeostasis are associated with metabolic syndrome and insulin resistance in Romanian and French populations

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Introduction
Zinc homeostasis is involved in numerous physiological and pathological conditions, ranging from type 1 and type 2 diabetes to memory impairment and cancer, and is determined by at least 28 genes, including 24 SLC *(Solute Carrier)* family members and 4 MTs (*Metallothioneins)*. To explore the potential role of zinc homeostasis in MetS *(metabolic syndrome)* and IR *(insulin resistance)*, we investigated 28 candidate genes by gene-SNPing.
Methods
A number of 1304 SNPs (*single nucleotide polymorphism*) were genotyped with the *Affymetrix* MEDISCOPE GeneChip in 483 subjects (123 cases of MetS and 360 controls) from two ethnic European populations – Romanian and French (MEDIGENE collection). Genetic association was tested by logistic regression, whereas quantitative variables were tested by correlation trend test. Bonferroni correction and false discovery rate were applied.
Results
The most significant association was found with MetS and concerned 3 SNPs located on *Chr10* between SLC39A12 and CACNB2 genes: rs7083207, rs17602947 and rs7903081 (Bonferroni $P<0.03$) with OR 2.15, 95% CI [1.5-3.0], OR 2.07, 95% CI [1.46-2.95] and OR 1.99, 95% CI [1.43-2.78], respectively. These 3 SNPs were also associated and/or correlated with the different components of MetS, notably with hypertriglyceridemia (OR 2.09, 95% CI [1.42-3.07], $P<7.8\times10\text{-}5$), but not associated with IR, nor correlated with HOMA-IR index of IR. The most significant association with IR was found for SLC39A11 gene located on *Chr17* (OR 2.95, 95% CI [1.68-5.18], Bonferroni $P<0.05$), which was also concordantly correlated with low HDL cholesterol and HOMA-IR.
Conclusions
Genes involved in zinc homeostasis are good determinants of MetS and IR, although different genes are implicated. SLC39A12/CACNB2 on *Chr10 and* SLC39A11 on *Chr17* were the most concordantly associated and correlated with MetS and IR, respectively.

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P334

Low iliac skinfold thickness predict mortality in a prospective cohort of white males

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Introduction
Obesity is a major risk factor for mortality from a range of causes. We investigated whether skinfold measurements predict mortality independently of variation in body mass index (BMI).
Methods
A prospective analysis of mortality in 870 apparently healthy adult Caucasian men participating in an occupational health cohort was undertaken. At baseline, skinfold measurements were taken at biceps, triceps, iliac and subscapular sites. Measurements were standardised for analysis. Derived measurements included the sum of all 4 skinfolds and subscapular to triceps, subscapular to biceps and BMI to iliac ratios. Outcomes considered included all-cause mortality and cancer, atherovascular, infection, and other deaths. Prediction of all-cause mortality was by Cox proportional hazards modelling. Competing risks analysis was used to assess predictors in specific mortality categories.
Results
There were 303 deaths during a mean of 27.7 years follow up. BMI predicted all-cause mortality and each mortality category except infection death. On multivariable analysis, with inclusion of age, BMI, smoking, alcohol and exercise, low iliac skinfold thickness independently predicted all-cause mortality (HR 0.77, 95% CI 0.66-0.90, $P=0.002$). Other predictors of all-cause mortality were subscapular to iliac ratio (HR 1.18, 95% CI 1.04-1.35, $P=0.011$), BMI to iliac ratio (HR1.25, 95%CI 1.08-1.45, $P=0.002$) and sum of all skinfolds

(HR 0.77, 95%CI 0.65-0.92, $P=0.004$). Low iliac score and a high BMI to iliac ratio also predicted mortality, atherovascular and infection deaths. In multivariate analysis, low iliac emerged as the most prominent skinfold predictor of mortality. Among participants with BMI$30 kg/m^2, iliac skinfold of $\leq$90 mm was associated with a six-fold increase in all-cause mortality risk.

Conclusion

Low iliac skinfold thickness, raised BMI to iliac ratio and raised subscapular to iliac ratio are independent risk factors for all-cause mortality in adult white males. A low iliac skinfold thickness is particularly important in obesity and its role requires further investigation.

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P335

Investigating the role of Annexin A1 in Adipogenesis and its ability to dampen Obesity associated Inflammation

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Introduction

Obesity results in an imbalance of systemic adipokines as well as pro and anti-inflammatory biomarkers. The attenuation of anti-inflammatory proteins, including Annexin A1 (AnxA1) in human obesity, may be a contributing factor to the chronic inflammatory phenotype which results. However, increased AnxA1 mRNA and protein levels in mature adipocytes suggest an additional role for AnxA1 in adipose tissue biology.

Aims

1) To investigate the role of AnxA1 in adipogenesis. 2) To investigate the effects of AnxA1 treatment on inflammatory biomarkers in an obese phenotype.

Methods

1) SGBS preadipocytes were differentiated with or without 10μM FPR2/ALX receptor antagonist; WRW4 for 14 days. Lipid accumulation was assessed by Oil Red O stain, imaged and analysed using Image J. 2) Differentiated SGBS cells were treated with 10 μM Ac 2-26 peptide and incubated in normoxic (21% O_2) or hypoxic (1% O_2) conditions for 24 hours to achieve obesogenic conditions. Gene expressions were analysed via RT-qPCR and normalised against GAPDH. Statistical analysis was preformed using GraphPad Prism version 5. Statistical significance was determined using T test at 95% level.

Results

1) Lipid accumulation significantly decreased in adipocytes differentiated with WRW4 compared to control cells (11.42 ± 5.157 SD, 13.92 ± 5.867 SD, $P=0.0092$ $n=6$, respectively). However, increased expression of genes regulating lipogenesis (SREB, PPARγ, ACC, FAS and GPAT) were observed in adipocytes treated with WRW4. 2) Treatment with Ac 2-26 peptide significantly decreased adipocyte specific proinflammatory biomarkers; Adipsin (0.325 ± 0.335, $P=0.0025$, $n=4$), Resistin (0.139 ± 0.073, $P<0.0001$, $n=4$) and Leptin (0.381 ± 0.507, $P=0.027$, $n=4$) in obesogenic cell model.

Conclusion

1) Endogenous AnxA1 may act through FPR1 to decrease lipid accumulation and adipogenesis. 2) The AnxA1/FPR2 receptor pathway could be used as a therapeutic mechanism to dampen obesity induced inflammation.

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P336

Metabolic phenotype of Male Obesity-associated Secondary Hypogonadism pre- and post-replacement therapy with intra-muscular Testosterone undecanoate therapy

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Aim

To explore the metabolic phenotype of Male Obesity-associated Secondary Hypogonadism (MOSH) and following treatment with long-acting intramuscular (IM) testosterone undecanoate.

Methods

A prospective observational pilot study on metabolic effects of IM testosterone undecanoate in MOSH (Hypogonadal [HG] group, $n=13$), including baseline comparisons with controls (Eugonadal [EG] group, $n=15$). Half the subjects ($n=7$ in each group) had Type 2 Diabetes Mellitus (T2D). Baseline metabolic assessment on Human Metabolism Research Unit (HMRU): fasting blood samples; BodPod (body composition), and; whole-body indirect calorimetry. The HG group was treated with testosterone undecanoate IM therapy for 6-29 months (mean 14.8-months [SD 8.7]), and HMRU assessment repeated. T-test comparisons were performed between baseline and follow-up data (HG group), and between baseline data (HG and EG groups). Data reported as mean (SD).

Results

Mean duration of Testosteorone IM therapy was 14.8 months (SD 8.7). Following Testosterone replacement IM therapy, there was a statistically significant reduction in fat mass (3.5Kg, $P=0.03$) and increase in lean body mass (2.9Kg, $P=0.03$). Overall, Testosteorone IM therapy resulted in a statistically significant improvement in HbA1C (9 mmol/mol, $P=0.03$), with 52% improvement in HOMA%B. Improvement in glycaemic control was driven by the HG subgroup with T2D, with 18 mmol/mol [$P=0.02$] improvement in HbA1C. Lipid profiles and energy expenditure were unchanged following Testosterone IM therapy. Comparisons between baseline data for HG and EG groups were equivalent apart from differences in testosterone, SHBG, BMR and vitamin D.

Conclusion

In patients with MOSH and T2D, Testosterone IM therapy improves body composition, beta cell function and glycaemic control.

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P337

Effect of Roux-en-Y bariatric surgery on lipoproteins, insulin resistance, and systemic and vascular inflammation in obese patients with and without diabetes

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Background

Obesity is a major modifiable risk factor for cardiovascular disease. Bariatric surgery is considered to be the most effective treatment option for weight reduction in obese patients with and without type 2 diabetes.

Aims

To evaluate changes in lipoproteins, insulin resistance, mediators of systemic and vascular inflammation and endothelial dysfunction following Roux-en-Y bariatric surgery in obese patients with and without diabetes.

Methods

Lipoproteins, insulin resistance, mediators of systemic and vascular inflammation, and endothelial dysfunction were measured in 27 obese patients with ($n=11$) and without type 2 diabetes ($n=16$), before and, six and twelve months after Roux-en-Y bariatric surgery.

Results

There were significant reductions in body mass index, waist circumference, small dense LDL apoB, fasting glucose, HbA1c, insulin HOMA-IR, hsCRP, TNFα, IL-6, MCP-1, ICAM-1, E-selectin and leptin and a significant increase in adiponectin 6 months after surgery. HOMA-IR, resistin, MCP-1 and ICAM-1 were further significantly reduced at 12 months, only in the diabetic group.There is a positive correlation between the relative proportional reduction in change in insulin resistance and the proportional change in resistin levels and a positive correlation between the proportional change in BMI and proportional change in leptin.

Conclusion

Lipoproteins, insulin resistance, mediators of systemic and vascular inflammation, and endothelial dysfunction improve after bariatric surgery in obese patients with and without diabetes. Insulin resistance and mediators of vascular inflammation continue to improve beyond 6 months in patients with diabetes. For the first time, we report a positive correlation between a decrease in insulin resistance and change in resistin levels and also between change in BMI and proportional change in leptin.

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Body fat distribution by dual energy x-ray absorptiometry (DXA) and metabolic risk factors in intravenous glucose tolerance test (IVGTT)-defined high and low insulin sensitivity normoglycaemic, overweight men

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Background
Increased adiposity is associated with increased cardiovascular disease (CVD) risk but among overweight individuals clarification is needed of relationships between insulin sensitivity, fat distribution and metabolic health that might contribute to this risk.
Methods
During the Heart Disease and Diabetes Research Indicators in a Screened Cohort (HDDRISC) study, 560 employment cohort normoglycaemic (FPG less than 7 mmol/L) Caucasian men (mean age 49.9 years, BMI 25.4 kg/m^2) received measurements of insulin sensitivity, Si, by IVGTT minimal model analysis. High or low insulin sensitivity was defined according to whether the value for Si was, respectively, above or below the median . Measurements of Si plus DXA body fat and CVD risk factors were recorded for 272 participants . Overweight was defined according to the cohort's BMI distribution and its associated CVD mortality risks. DXA and risk factor characteristics in overweight participants were compared between those with higher or lower Si.
Results
Median Si was 3.0 $min^{-1}.mU^{-1}.L$ and BMI $\geq$ 27 kg/m^2 was considered overweight. Of the 272 potential participants, 78 were overweight (median BMI 28.8, interquartile range 27.7-30.5 kg/m^2) with 55 located in the lower Si and 23 in the higher Si groups. The two groups did not differ in age, BMI, blood pressure, total cholesterol, uric acid, FPG, smoking, exercise, alcohol or medication. The higher Si group had lower median LDL cholesterol (3.13 vs 3.47 mmol/L, $P=0.008$) and, triglycerides (1.19 vs 2.22 mmol/L, $P=0.003$) and higher HDL cholesterol (1.30 vs 1.12 mmol/L, $P=0.02$). DXA fat masses did not differ between the groups but the higher Si group had a lower percentage of android fat (53.0 vs 56.4%, $P=0.03$).
Conclusions
In overweight Caucasian men, there is marked variation in insulin sensitivity, with higher insulin sensitivity associated with lower percent android fat and a more favourable CVD risk factor profile. This heterogeneity supports differentiation of metabolically healthy and unhealthy overweight and obesity.

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The Prevalence of Obstructive Sleep Apnoea in women with Polycystic Ovary Syndrome: a Systematic Review and Meta-analysis

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Background
Obesity is a common risk factor for obstructive sleep apnoea (OSA) and polycystic ovary syndrome (PCOS).
Objective
To examine the prevalence of OSA in women with PCOS.
Search sources
Electronic databases [Medline, Embase, Cinahl, PsycInfo, Scopus, Web of Science, Opengrey, and Cochrane Central Register of Controlled Trials], conference abstracts, and reference lists of relevant articles. The search was not restricted by language or publication status.
Main results
Fifteen studies involving 568 participants were included. OSA prevalence in women with PCOS was 36.1% (95% CI: 22.4% – 51.0%).
There was a trend for higher OSA prevalence in studies from the USA than those from other countries (43.2% v. 25.2%), and in women compared to adolescent girls with PCOS (46.8% vs. 21.2%), though not statistically significant. The definition of PCOS did not significantly alter OSA prevalence.
In the two studies that stratified prevalence estimates by body mass index, OSA prevalence was 38% higher in women with PCOS and obesity compared to those without obesity (prevalence difference: +37.9%, 95% CI: 15.0% - 60.9%).
Limitations
The majority of studies were found to be at high risk of selection bias; did not account for important confounders; included largely women with class II obesity; and were conducted in the USA. None of the studies were population based. There was a statistically significant heterogeneity among the studies.
Conclusions
OSA appears to have a high prevalence in obese women with PCOS. The true prevalence of OSA in women with PCOS is not known. Whether women with PCOS are at increased risk of OSA, compared to women without PCOS, is also unknown. Well conducted, large, cohort studies are required to assess the true prevalence of OSA in women with PCOS, and to examine the natural history and impact of OSA in women with PCOS.

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Vitamin D status before and after bariatric surgery during 4 years of follow-up

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Background
Bariatric surgery for severe obesity can lead to micronutrient/vitamin deficiencies.
Aim
To study baseline and post-surgical prevalence of vitamin D deficiency in patients undergoing bariatric surgery.
Setting
University teaching hospital in North-West England.
Methods
We performed an observational cohort analysis of longitudinal data on vitamin D and related parameters in patients who underwent bariatric surgery. Patients were routinely recommended daily combined calcium and vitamin D supplementation post-surgery.
Results
We studied 480 patients with a median age of 48.8 years, weight 139.3 kg and body mass index 49.3 kg/m^2 who underwent gastric bypass (277; 58.9%), sleeve

Table 1 Outcome measures after bariatric surgery

Outcome measures†	0 months	12 months	24 months	36 months	48 months
Body mass index (kg/m^2)	49	34****	34****	36****	37****
Vitamin D (nmol/l)	30	57****	56****	50****	53****
Parathyroid hormone (pmol/l)	5.0	5.4	5.3	5.5	5.6
Corrected calcium (mmol/l)	2.33	2.29	2.28****	2.24****	2.28****
Phosphate (mmol/l)	1.05	1.14****	1.09	1.07	1.10
Alkaline phosphatase (U/l)	81	82	77	83	78

†Median | ****$P<0.0001$ (compared to baseline)

gastrectomy (168; 35.7%) or other primary bariatric surgery (25 patients; 5.3%). Median vitamin D level was significantly lower at baseline and improved with supplementation post-surgery (Table 1). Whereas 52.8% had vitamin D deficiency (<30.0 nmol/l) and 25.1% insufficiency (≥30.0 <50.0 nmol/l) preoperatively, 13.3 and 23.0% had deficiency and insufficiency, respectively, at 12 months with similar trends up to 4 years of follow-up.
Conclusion
Vitamin D deficiency and insufficiency were commonly prevalent pre-surgery, which reduced significantly with routine supplementation post-surgery.
Table 1

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Resistant Hypertriglyceridemia in pregnancy

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Case
A 34 years old lady presented to the antenatal clinic at 7 weeks gestation with unplanned pregnancy. She had background history of HTN, poorly controlled T2DM and hypercholesterolemia . She continued taking metformin, gliclazide, sitagliptin and simvastatin which were stopped at the booking appointment . Metformin continued and started on insulin. Blood tests at booking showed HbA1c 126, Cholesterol 5.2 , Triglycerides 2.7. She was started on thyroxine for subclinical hypothyroidism. During the course of treatment her insulin requirements increased with gradual improvement in HbA1c at 76 mmol/mol at insulin dose of >300 units/day. At 28th week gestation, she presented with abdominal pain and found to have Cholesterol of 12.9 mmol/L, Triglycerides 54.5 mmol/L with normal HDL, LDL and amylase. Abdominal USS was unremarkable. She was started on dietary restriction along with metformin, heparin and intravenous insulin which was discontinued after triglycerides improved to <11 mmol/L with improved glucose. Her triglycerides increased again immediately after IV insulin discontinued and therefore insulin was restarted. Once triglycerides improved , she was started on Fenofibrate and omega3 acid alongwith adjustment of sc insulin dose at 420 units/day and heparin. Subsequent tests showed triglycerides again at 20 mmol/L with hyperglycemia, it was therefore decided for her to have early delivery at 32 weeks by C-section and an alive healthy baby born with no complications. Lipid profile the next day showed triglycerides at 4.5 mmol/L with improved blood glucose levels.
Discussion
Pregnancy induced hypertriglyceridemia is rare condition associated with risk of life threatening complications. Estrogen induced increase in lipoprotein production and decrease lipoprotein lipase activity in the liver can cause hypertriglyceridemia in pregnancy with more profound increase during the 3rd trimester. There is need to have case based longitudinal studies due to lack of formal guidelines for management.

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Anthropometric changes associated with antiretroviral therapy in nigerians infected with human immunodeficiency virus

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Background
Human immunodeficiency virus (HIV) infection and the Acquired Immune Deficiency Syndrome (AIDS) are health problems with infected individuals frequently manifesting some abnormalities including significant weight loss. This has been associated withtumor necrosis factor alpha and interleukin 1β production by circulating mononuclear white blood cells in patients with HIV infection andaltered metabolism due to cytokine dysregulation and metabolic demands of antiretroviral medication.
Objective
To determine the changes in anthropometric variables 6 months after initiation of antiretroviral therapy in HIV infected subjects.
Materials and methods
The study was a longitudinal study involving 150 newly diagnosed, drugnaïve HIVpositive subjects who met the criteria for initiating antiretroviral therapy.They had their anthropometric measurements inclusive of weight, body mass index, waist circumference, hip circumference,mid upper arm circumference and skinfold thickness determined before initiating the medications.These patients were followed up and the same measurements repeated 2 monthly for 6 months Data analysis was by SPSS version 2.0 using frequency and paired sample T test.Significance of differences was set at $P<0.05$.
Results
Sixteen subjects were lost to follow up by the end of 6 months.In our study, 80% gained weight, 15.5% had a stable weight and 4.5% lost weight.The table below summarizes the anthropometric changes after 6 months.There were statistically significant increase in the mean of the variables determined at 6 months.
Conclusion
Highly Active Antiretroviral Therapy (HAART) as treatment for HIV/AIDS in addition to reducing the morbidity and mortality associated with the disease,also improves wellbeing by restoration of weight loss.

Variables	Baseline (mean ±s.d.)	6month (mean ±s.d.)	*P* value
Weight (kg)	65.80±14.00	69.11±13.69	<0.001
BMI (kg/m^2)	23.57±4.55	24.75±4.39	<0.001
Waist circumference (cm)	81.46±11.72	86.32±12.37	0.02
Hip circumference (cm)	98.09±9.79	102.65±10.18	0.04
Mid upper arm circumference (cm)	28.7±4.74	34.3±6.15	0.012
Mid thigh circumference (cm)	50.26±7.56	56.62±8.76	0.023
Biceps (mm)	11.13±4.75	16.10±6.50	<0.001
Triceps (mm)	17.90±9.07	23.10±9.67	<0.001
Suprailiac (mm)	19.26±9.56	24.19±10.60	0.013
Subscapular (mm)	16.32±6.84	20.52±8.54	0.014

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The challenges of reducing calorie intake in everyday life- a pilot study

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One of the major risk factors for type 2 diabetes is Obesity (accounts for 80-85% of overall risk of developing type 2 diabetes). The UK is currently amid an obesity epidemic and it is recommended that the UK population reduce their daily calorie intake. As people are surrounded by food, it was acknowledged that this can be challenging to achieve on a long-term basis. This pilot study aimed to identify common social cues that encourage people to increase their calorie consumption- and how this varies between different ethnic groups- and to see if short term calorie reduction can cause significant weight reduction.
A group of 12 participants who fitted the inclusion criteria (average daily calorie intake > 1500 kcal, no medical problems and aged between 18-30) were asked to reduce their average daily calorie intake by 20%. They were not allowed to exceed it for 7 days and had to record the challenges they faced during the task. They also measured their weights before and after the challenge.
The study does show that there is weight reduction with short term calorie reduction. Interestingly, the data shows a downward trend ie: the bigger the calorie reduction the smaller the weight reduction. The commonest social cues mentioned were: easily accessible treats (29%), home environment (21%) and university related work (21%). 85.7% of south Asian participants involved in this study exceeded their calorie allowance at least once during the challenge, whereas only 50% from non-south Asian community exceeded the allowance at least once, illustrating that certain communities were influenced more by the common social cues identified. The study does show that if carried out appropriately, short term calorie reduction can cause weight loss which eventually can reduce obesity amongst UK population.

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Metabolic profile in a semi urban community in South western Nigeria

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Introduction
The number of people with type 2 diabetes is increasing worldwide. Currently, 415 million adults have diabetes worldwide and It has been projected that this will increase to 642 million people by 2040. Several important risk factors have been linked to the development of type 2 diabetes, the most important of which is excess body weight.
This study set out to determine the blood glucose levels of people in a semi urban community and relate it with the markers for obesity.
Methodology
This was a cross sectional study of subjects living in Owo, a semi urban community in South western Nigeria. Weight, height, waist circumference, hip circumference, blood pressure and random blood sugar measurements were done using standard methods. Data was analyzed with SPSS version 21.0. Descriptive statistics were done. Associations were explored using Pearson correlation at 5% level of significance.
Results
A total of 106 subjects were screened. Of these, 84 (79.2%) were not known to have diabetes previously. There were 26 (31%) males and 58 (69%) females giving a male to female ratio of approximately 1:2. The mean age of subjects was 50.6 + 15.4 years. Only one (1.2%) of the subjects had RBS $>$11.1 mmol/L. The mean BMI of subjects was 24.7$\pm$5.3 kg/m2. Seven (8.3%) of the subjects were underweight while normal weight and overweight/obesity were found in 40 (47.6%) and 37 (44.1%) of the subjects respectively. The mean waist circumference in male and female subjects were 77.1$\pm$9.5 cm and 84.0$\pm$12.6 cm respectively. Their mean SBP was 135.1$\pm$22.3 mmHg while DBP was 85.4$\pm$13.7 mmHg.
There was a positive correlation between random blood glucose and waist circumference (r=0.200, P=0.069). A positive correlation was also found between the body mass index and waist hip ratio (r=0.202, P=0.065).
Conclusion
The proportion of people in the general population who are overweight to obese is high. These are at increased risk of developing type 2 diabetes. Public health enlightenment on this should be intensified.

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The challanges faced in managing gycogen storage disease

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Glycogen storage disease, which is a metabolic disorderof glycogen storage, affecting 1 in 20000-40000 ive births. This is a case of yound adolescent female with glycogen storage disease type1b, presented with lactic acidosis and managed in ITU.
18 years old femae from Honk kong, student in a college, admitted to a dgh hospital with fever, vomiting and abdominal pain for a week. examination showed severe features of dehydration, hypotension and tachycardia. her blood gases showed ph od 7.35, bicarbonate was 15.5, lactae was 10.3, amylase was 46, was started on i/v fuids and admitted in a medical ward. while in the ward, patient deteriorated with persiting vomiting and hypoglycemia despite i/v dextrose.She was transferred to itu, started parenteral feeding, i/v pabrinex and 10% dextrose. was seen by dietician and special diet with cornstarch was started. while in itu , had neutropenia, fever spikes and stared on antibiotics for neutropenic sepsis.despite above , patient continued to have hypoglycaemia and parenteral feeding continued with dextrose i/v. as patient became stable, moved to a ward and continued monitoring blood sugar, neutrophil and lactate.
The challanges faced in managing glycogen storage diseases 1b are severe infection due to neutropenia and functional defects in neutrophils and monocytes. they may deveop concomitent kidney disease, otitis media nd diarrhoea.hypoglycaemia can be difficult to manage due to poor compliance with diet. They may require liver transplant as well. They are best followed up in specialist tertiary care centres with experts on metabolic diorders.

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Reproduction

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Mass spectrometry-based assessment of androgen excess in 1205 consecutive patients over 5 years: PCOS most common diagnosis, but severe androgen excess indicates other ovarian and adrenal pathology

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Androgen excess in women is most commonly caused by polycystic ovary syndrome (PCOS), but sinister ovarian and adrenal pathology requiring immediate action needs to be excluded. Here we examined whether the severity of androgen excess indicates the likely underlying pathology in women evaluated for androgen excess.
We included all women undergoing assessment of serum DHEAS, androstenedione (D4) and testosterone (T) by liquid chromatography-tandem mass spectrometry at the University Hospital Birmingham from 2012-2016. All patients with at least one androgen increased above the reference range were phenotyped by clinical notes review, including ascertainment of an underlying diagnosis likely to cause androgen excess.
A complete serum androgen profile was available in 1205 women; at least one of the three androgens was increased above the sex- and age-specific reference range in 378 patients (31.4%; 303 pre-and 75 postmenopausal). Recorded diagnoses included: PCOS (n=293=76%); congenital adrenal hyperplasia (CAH; n=18=5%), adrenocortical carcinoma (ACC; n=15=4%), ovarian hyperthecosis (OHT; n=7=2%), Cushing's disease (n=7=2%), ovarian tumour (n=2=0.5%), adrenocortical adenoma (n=2=0.5%), and unknown (n=22=6%). Increased androgens were divided into 3 concentration ranges according to severity. In premenopausal women, PCOS was the most likely diagnosis at any level of androgen excess (prevalence 75-97%), except at Level 3 T ($>$5 nmol/L) and Level 3 A4 excess ($>$16.5 nmol/L), where CAH and ACC were more prevalent. In postmenopausal women, PCOS was the commonest diagnosis only at Level 1 T excess; ACC and OH were the most prevalent diagnoses at Level 3 excess (T$>$5 nmol/L, D4$>$13 nmol/L, DHEAS$>$20 mmol/L).
Patterns and severity of hyperandrogenism predict the likelihood of non-PCOS pathology. CAH and ACC should be considered in Level 3 T or A4 excess in premenopausal women, and ACC and OHT in Levels 2 and 3 androgen excess in postmenopausal women. These data provide clinical guidance for the need of further work-up to identify non-PCOS causes of androgen excess.

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A comparison of Ovarian Hyperstimulation Syndrome (OHSS) parameters following different triggers of oocyte maturation during IVF Treatment

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Background
IVF is an effective treatment for infertility, however it may be complicated by the potentially life-threatening 'ovarian hyperstimulation syndrome' (OHSS). OHSS is an iatrogenic condition, resultant on the mode of triggering oocyte maturation. Kisspeptin safely triggers oocyte maturation in women at high risk of OHSS, but has yet to be compared with current triggers of oocyte maturation (hCG or GnRH agonist).
Methods
We compared parameters of early OHSS (2-5 days after oocyte retrieval) after different triggers of oocyte maturation (hCG, GnRH-agonist or kisspeptin) in women at high risk of OHSS at Hammersmith Hospital, London, UK between 2013-2016. Inclusion criteria included antral follicle count $23, age $<$35 yrs, BMI $<$30 kg/m^2 and both ovaries intact. Participants received either kisspeptin (n=115), GnRH-agonist (GnRHa) (n=94) or hCG (n=22) to trigger oocyte maturation. OHSS screening comprised of sonographic measurements (ascitic fluid and ovarian volume), OHSS symptoms and biochemical parameters. Groups were compared using one-way ANOVA with post-hoc Bonferroni correction.

Results
OHSS symptoms were least frequent following kisspeptin, and most frequent after hCG triggering: abdominal pain occurred in 80% of patients after hCG, 22% after GnRHa, but only 12% after kisspeptin. Vomiting was also most frequent following hCG (10%) and least common following kisspeptin (1%). Mean ovarian volume (±SD) 3-5 days following oocyte retrieval was significantly larger following hCG (192±97 mls) than GnRHa (53±37 mls; $P<0.0001$), and significantly smaller still following kisspeptin (9±4 mls; $P<0.0001$), suggesting ovarian recovery is most rapid following kisspeptin. Mean ascitic volume (102±150 mls) was greater following hCG triggering than after either GnRHa (5.8±22 mls), or kisspeptin (4.6±7.8 mls; $P<0.0001$).
Conclusion
We observe that signs and symptoms of OHSS are significantly less common following kisspeptin triggering than either hCG or GnRH agonist in a population at high risk of OHSS. Kisspeptin may thus offer a safer therapeutic option to trigger oocyte maturation particularly in women at high risk of OHSS.

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Polycystic ovary syndrome is associated with adverse mental health and neurodevelopmental outcomes: a retrospective, observational study

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Background
Polycystic ovary syndrome (PCOS) is characterised by hyperandrogenism, oligo/amenorrhoea and subfertility but the effects on mental health outcomes are unclear. Offspring neurodevelopment might also be influenced by gestational androgen exposure.
Aims
To determine if (i) there is an association between PCOS and psychiatric outcomes, and (ii) rates of autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) are higher in the offspring of mothers with PCOS.
Methods
Data were extracted from the Clinical Practice Research Datalink. Patients with a diagnosis of PCOS (2000-2014) were matched to two control sets (ratio 1:1) by age, BMI and primary care practice. Control set 2 were additionally matched on prior mental health status. Primary outcomes were the incidence of depression, anxiety and bipolar disorder. Secondary outcomes were the prevalence of ADHD or ASD in offspring. Rates of progression to each primary outcome were compared using Cox proportional hazard models. Prevalence of ADHD and ASD in offspring were compared using logistic regression.
Results
16,986 eligible PCOS patients were identified; 16,938 (99.7%) and 16,355 (96.3%) were matched to control sets 1 and 2 respectively. Compared to control set 1, baseline prevalence was 23.1% versus 19.3% for depression ($P<0.001$), 11.5% versus 9.3% for anxiety ($P<0.001$) and 3.2% versus 1.5% for bipolar disorder ($P<0.001$). The hazard ratio for time to each endpoint was 1.26 (95% CI 1.19-1.32; $P<0.001$), 1.20 (1.11-1.29 $P<0.001$), and 1.21 (1.03-1.42; $P<0.001$) for cohort 1 and 1.38 (1.30-1.45 $P<0.001$), 1.39 (1.29-1.51 $P<0.001$) and 1.44 (1.21-1.71) for cohort 2. The odds ratio for ASD and ADHD in offspring were 1.54 (1.12-2.11) and 1.64 (1.16-2.33) for cohort 1, and 1.76 (1.27-2.46) and 1.34 (0.96-1.89) for cohort 2.
Conclusions
PCOS is associated with psychiatric morbidity and increased risk of ADHD and ASD in the offspring. Screening for mental health disorders should be considered during assessment.

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Metformin improves oestrous cycle, ova count and expression of oestrogen receptors in diabetic female Sprague-Dawley rats.

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The female reproductive system provides several functions. These include ovulation, pregnancy and childbirth. The incidence of diabetes mellitus (DM) is increasing rapidly worldwide and it is associated with reproductive complications. Metformin is an oral hypoglycaemic drug used in the management of DM. The present study determined the effect of metformin on some reproductive function in alloxan-induced diabetic female Sprague-Dawley rats.
Rats were divided into four groups; (1) Untreated non-diabetic control (drug vehicle), (2) Untreated diabetic (drug vehicle), (3) Treated non-diabetic (metformin 100 mg/kg); and (4) Treated diabetic (metformin 100 mg/kg). Diabetes was induced with alloxan in the rats followed by a six-week treatment with metformin. The pattern of the oestrous cycle, followed by the ova count were observed and recorded. Plasma levels of oestradiol, progesterone, follicle stimulating hormone and luteinizing hormone were measured. Oxidative stress parameters and expression of oestrogen receptors (ERβ) in the ovaries were also determined.
Diabetes caused a significant increase ($P<0.05$) in the frequency of proestrus, oestrus, ova count, and expression of ERβ receptor. In the ovary, the levels of antioxidant enzymes - catalase and glutathione were reduced. However, after metformin treatment, expression of the receptor was increased. Metformin treatment also increase the ova count, frequency of the proestrus and oestrous phases, with a significant decrease in the diestrus phase in the treated diabetic group. Plasma level of reproductive hormones (oestrogen, LH and FSH) were unchanged after metformin treatment of diabetic rats except for progesterone that was returned to control level. In addition, there was an improved antioxidant status in diabetic rats following metformin treatment.
In conclusion, the result of the present study showed that metformin can improve on some reproductive function in the diabetic state; and so, more consideration should be given to its non-hypoglycaemic effects and its use in the management of reproductive complications associated with DM.

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RNA-Sequencing reveals a downregulation of cholesterol metabolism pathways in granulosa cells from women with PCOS

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Polycystic ovary syndrome (PCOS) is a common endocrinopathy that is associated with anovulatory infertility, menstrual disturbances and an adverse metabolic profile. Although the pathophysiology of PCOS remains unclear, dysregulation of gene expression has been previously shown in theca and granulosa cells. In this study, we used RNA-Sequencing to compare the transcriptomes of human granulosa cells from women with and without PCOS. Granulosa cells were retrieved during egg collection for in-vitro fertilisation from women with normal ovaries and regular cycles and women with polycystic ovaries and irregular cycles. RNA was extracted and processed for RNA-Sequencing. Quantitative PCR was used to validate changes in gene expression. RNA-Sequencing identified 21175 genes expressed in human granulosa cells. Of these, 450 genes were differentially expressed in women with PCOS ($P<0.05$, after controlling for multiple comparisons). Gene Ontology and Reactome pathway analysis highlighted a group of genes involved in cholesterol biosynthesis and metabolism that are highly enriched (19-fold increase, $P<1.60E-16$) in granulosa cells from women with PCOS. In total, a group of 21 cholesterol biosynthesis and metabolism genes were identified, and interestingly all showed reduced expression. These include downregulation of Hydroxy-3-methylglutaryl CoA synthases 1 and 2 (HMGCS1, 8-fold, P

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Impact of delayed pubertal induction and route of estrogen administration on health parameters in adults with Turner Syndrome

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Background
The Turner Syndrome Life Course Project, UCLH, has collected data on 810 women with TS, attending clinic for 20 years and has accumulated over 8000

clinic visits. We present an analysis of the effects of timing and type of exogenous oestrogen on health outcomes in adults.
Methods
A cross- sectional analysis of 475 subjects with primary amenorrhoea with accurate age of pubertal induction data was performed using correlation coefficients controlling for age.
A second univariate analysis inclusive of individuals with secondary amenorrhea, using data from 5225 clinic visits was performed to assess the effect of oestrogen type on medical endpoints. Age and BMI were controlled for. Hormone replacement therapies (HRT) were categorised as combined oral contraceptive (OCP; $n=1526$) clinic visits, oral oestrogens (combined 17B estradiol and conjugated equine oestrogens; $n=3036$) and transdermal 17B estradiol ($n=663$).
Results
Median (90th centiles) age of pubertal induction was 14 years. Oestrogen start age correlated with hip and spine T-score ($P=<0.01$). Differences in medical endpoints for three types of HRT included raised liver enzymes (AlkP, ALT, GGT) associated with transdermal estradiol compared to oral oestrogens and OCP users ($P=<0.01$). Blood pressure was elevated in the OCP users compared to oral and transdermal oestrogen users ($P=<0.01$). Bone density was greater in transdermal estradiol users compared to OCP and oral oestrogens users ($P=<0.01$).
Conclusions
An earlier oestrogen start age was associated with greater bone density. This data supports an earlier age of pubertal induction before age 14.
Whilst bone density was greater in transdermal users, this group also experience elevated liver enzyme parameters. Therefore there may be a trade off when considering oral versus transdermal in the management of TS.
OCP users experience higher blood pressure. Given the propensity of women with TS to develop hypertension ethinylestradiol is contraindicated.

	OCP	Oral oestrogen	Patch
AlkP	79.6	84.1	98.6*
ALT	27.4	28.7	35.4*
GGT	45.5	42.7	57.3*
DBP	75.2*	72.9	27.7
SBP	124.7*	119.9	120.2
Spine T	−1.1	−1.09	−0.81*
Hip T	−0.85	−0.9	−0.7*

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P357

Metabolic syndrome reduce gravid uterine contractility in female sprague-dawley rat

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Metabolic syndrome is a clustering of several cardiovascular risk factors including obesity, hypertension, diabetes, high triglyceride etc. Obesity has been shown to decreases key markers of uterine contractility during parturition in the rat and diabetes is associated with impairment of uterine contractility and high caesarean section rate. In this study, the effect of metabolic syndrome on gravid uterine muscle contractility in sprague-dawley rat was determined.
Female sprague-dawley rats were fed control (CON, $n=10$) and Metabolic Syndrome were fed high salt and high-fat, high-cholesterol (HFHC) diet for 8 weeks and given 60 mg/kg streptozotocin i.P. to induce diabetes (METS, $n=10$). Animals were mated and, once pregnant, maintained on their diet throughout the experiment. On gestational day 15, rats were killed and a small portion of the uterine muscle was excised and transferred into an organ bath containing physiological salt solution for contractility studies. The organ bath was connected to a force transducer (Grass Model FT03) connected to the ADInstrument Power lab; the tension was adjusted. The transducer was pre-calibrated to give a 2 cm deflection for every 1 gram force. Spontaneous contractions were measured for various graded doses of oxytocin, acetylcholine and potassium chloride and the tension/force and duration of contraction calculated and recorded. Blood was collected for determination of plasma insulin, lipid profile, maternal corticotrophin releasing hormone (CRH), blood glucose, serum calcium and placenta CRH, were also determined. Body and fat depot weights were recorded.
Force and duration of contraction caused by oxytocin was significantly reduced ($P<0.05$) in MTES rats compared with the control. Acetylcholine and potassium chloride also produced a significantly reduced ($P<0.05$) force and duration of contraction in METS. Serum calcium, maternal CRH, insulin, blood glucose, triglyceride cholesterol, abdominal and retroperitoneal fats were all significantly increased ($P<0.05$).
In conclusion, METS impair uterine contractility by reducing the force and duration of uterine contraction.

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P358

Pregnancy, pre-eclampsia and vitamin D: a multi-scale mathematical approach

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Vitamin D deficiency during pregnancy has been linked to adverse pregnancy outcomes such as pre-eclampsia (PET), but continues to be defined by serum measurement of a single metabolite, 25-hydroxyvitamin (25(OH)D). To identify broader changes in vitamin D metabolism during normal and PET pregnancies we developed a mathematical model using a reduced reaction network for vitamin D metabolism that allows for complete parametrisation by multiple vitamin D metabolites. Serum vitamin D metabolites were analysed for a cross-sectional cohort of women from the West Midlands ($n=88$); which included normal pregnant women at 1st (NP1, $n=25$) and 3rd trimester (NP3, $n=21$) and pregnant women with PET ($n=22$), as well as non-pregnant female controls ($n=20$). Conventional statistical analysis showed no significant difference between NP3 and PET for serum concentrations of 25(OH) Dand 24, 25(OH) 2D3. However, the reaction network mathematical model revealed clear differences in vitamin D metabolic pathways between NP3 and PET groups. To assess the possible predicative value of this model, further studies were carried out using serum vitamin D metabolome data ($n=50$) from an early 2nd trimester pregnancy cohort (SCOPE Ireland study), of which 25 women went on to develop PET later in pregnancy. However, the mathematical model showed no significant difference between NP3 and PET cases at 15 weeks of gestation. These data indicate that mathematical modelling offers a novel strategy for defining the impact of vitamin D metabolism on human health. This is particularly relevant in the context of pregnancy, where major changes in vitamin D metabolism occur across gestation, and dysregulated metabolism was clearly evidenced in women with established PET. Further studies are required to determine the efficacy of mathematical modelling as a predictive tool for other adverse events in pregnancy, and for the broader impact of vitamin D on human health.

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P359

Is serial urinary progesterone measured via automated chemiluminescent assay a valid alternative to pregnanediol via manual ELISA for the detection of ovulation?

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Background
Urinary concentrations of the major progesterone metabolite pregnanediol glucuronide (P3G) are used clinically and in research to monitor ovulation.

This ELISA is laborious and costly. If it could be replaced by the automated sensitive chemiluminescence assays routinely used for serum this would be of great value.
Objective
We aimed to determine the validity of urine progesterone as measured by two widely used automated assays in comparison to the standard P3G assay.
Methods
Daily urine aliquots were obtained across 20 cycles (median (range) length 28(25–37) days in 14 women mean (SD) age 33.5(6.6) years. Ovulation was confirmed in all cycles by transvaginal ultrasound and serial LH measurement. Urine progesterone was measured and corrected for creatinine (uP4-Cr), by automated Abbott chemiluminescent microparticle immunoassay (CMIA) or Roche electrochemiluminescence immunoassay (ECLIA), compared with an in-house P3G ELISA (uP3G-Cr). Midfollicular (LH surge day-3 to day-10) and midluteal (LH surge day +3 to +10) phases were compared. Sensitivity and specificity were calculated by comparing midfollicular and midluteal samples, using a cutoff 1.5-fold increase in concentration.
Results
There was a luteal rise in all cycles in uP4-Cr (both assays) and in 19 cycles (95%) in uP3G-Cr. The median (range) luteal rise was 3.52 (1.16–7.92) for CMIA, 1.66 (1.09–2.45) for ECLIA and 4.81 (0.78–11.70) for uP3G-Cr. Aberrant rises in uP4-Cr above the luteal threshold were seen around the follicular phase with CMIA but not ECLIA.
Conclusions
Automated CMIA but not ECLIA progesterone assay demonstrated marginally inferior sensitivity to detect ovulation and superior specificity, compared with P3G manual ELISA. The reasons ECLIA showed spurious follicular rises, poorer correlation with P3G, sensitivity and specificity are not clear but may include a matrix effect. Serial urinary progesterone using ECLIA chemiluminescence demonstrates potential as an alternative to P3G.

	uP3G-Cr ELISA $\mu gmol^{-1}$	uP4-Cr ECLIA $nmolmol^{-1}$	uP4-Cr CMIA $nmolmol^{-1}$
Median (range) follicular concentration	16.00 (6.66–33.39)	1.55 (0.77–2.24)	0.70 (0.23–1.54)
Median (range) luteal concentration	92.48 (18.79–136.10)	2.35 (1.39–3.90)	1.99 (0.85–4.21)
Pearson Correlation vs P3G-Cr		0.40 (0.32–0.47) $P<0.0001$	0.64 (0.58–0.70) $P<0.0001$
Sensitivity	0.92	0.56	0.87
Specificity	0.83	0.81	0.86

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P360

Aberrant fetal development precipitated by genistein is accompanied with disruption in the Giant Trophoblast cell histomorphometry, and alteration in the serum, placenta and the amniotic fluid oxidation-reduction system

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Genistein is an endocrine-disrupting chemical (EDC), derived from soya, with reported adverse effects on fetal development. The placenta regulates fetal environment for fidelity of organogenesis which can be compromised by several external factors including EDCs. This study examined the influence of genistein on the histomorphometry of the Giant Trophoblast Cells (GTC) of the placenta and the oxidative stress balance across the maternal serum, placenta and the amniotic fluid at different gestational days.
Sixty-five pregnant Sprague Dawley rats were divided into control (Control) and genistein (Gen) force fed (2 mg/kg and 4 mg/kg) groups. At terminal gestation days raging (GD) 0, 6, 13, 18 and 20, the rats were sacrificed by cervical dislocation. Blood samples, amniotic fluid and placenta homogenates (PH) were carefully prepared and used for the antioxidant assays. Hematoxylin and eosin stained placenta tissue slides were prepared and used for GTC histomorphometry assessment under the microscope. All procedures used were in accordance with International best practices in animal care and experimentation as approved by the Institution Health Research and Ethics Committee.
Serum level of antioxidants; SOD, CAT, GSH were increase while their levels were reduced across GDs in AF, but the levels were fluctuating in the PH with a decrease in GSH and CAT. GTC population and zones in the placenta tissue were significantly reduced in all genistein treated groups.
Aberrant effect of genistein on fetal development was accompanied with reductions in GTC zone and count and with a disruption in the antioxidant defense system across the maternal serum, placenta and amniotic fluid in gravid laboratory rats.

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P361

Non-cardiac maternal and fetal outcomes in Turner Syndrome pregnancies.

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Background
Despite new, albeit draft, international guidelines there remains limited data and guidance on the non-cardiac obstetric management and outcomes in women with Turner Syndrome (TS).
AIMS
This retrospective single centre audit aimed to assess the maternal and fetal outcomes in a large single centre cohort.
METHODS
We identified 110 women under our care with TS. Of these, 28 women had attempted to achieve a pregnancy. Clinical data was correlated with birth registration records.
RESULTS
12/28 achieved a pregnancy using assisted reproductive techniques (ART), the other 16/28 achieved spontaneous conception (SP), 22 seperate pregnancies. Of those undergoing ART, 6/12 went on to have live births, including a set of twins. The genotype 45XO was expressed in 2/6 of the ART group; 4/6 expressed mosaicisms. Maternal age ranged from 31-40. There was no information available regarding frequency of donor oocytes. Pre-existing hypertension was present in 3/6, and there was no evidence of progression to pre-eclampsia. Gestational diabetes developed in 2/6, one of whom went on to develop Type 2 Diabetes.
Of the 16 who experienced SP, one woman expressed a 45XO genotype; 15 expressed mosaicisms. Full obstetric information was available on 6 of the SP maternities. There were 3 elective caesarean sections for obstetric indications and 3 operative vaginal deliveries. One woman developed gestational hypertension, and then pre-eclampsia in a subsequent pregnancy. One was known to have subclinical thyroid disease, but no new cases in pregnancy. No women developed gestational diabetes, obstetric cholestasis or acute cardiac problems. All 6 babies had a birth weight above the 10th centile.
Conclusions
Although pregnancy rates were low, outcomes were good. Accepting the increased risk of cardiac complications, perhaps it is time to reconsider our counselling of these women, in order to provide a more reassuring advice within the appropriate Multi Disciplinary Team setting.

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P362

Kisspeptin-leptin interplay in assisted reproductive techniques

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Background
Leptin facilitates onset of puberty by impacting hypothalamic Kisspeptin, gonadotropin releasing hormone, follicle stimulating and luteinizing hormone.

The link of peripheral Leptin-Kisspeptin in regulating the ovarian and endometrial tissue in relation to adiposity is unknown. Therefore, we wanted to identify their association with body mass index (BMI) and success of assisted reproductive treatments (ART) in infertile females.
Methods
A cross sectional study was carried from August 2014 till May 2015 after receiving ethical approval. The study group comprised of females with an age range of 25-37 year who had duration of unexplained infertility for more than two years. They were grouped as; underweight (<18 kg/m^2), normal weight (18-22.9 kg/m^2), overweight 23-24.99 kg/m^2 and obese (>25 kg/m^2). Kisspeptin and Leptin levels were measured by enzyme linked immune sorbent assay before down regulation of ovaries and initiation of treatment protocol of ART.Failure of procedure was detected by beta human chorionic gonadotropin <25 mIU/ml (non-pregnant) whereas females with levels >25 mIU/ml and cardiac activity on trans-vaginal scan were declared pregnant.
Results
Highest Kisspeptin and Leptin levels were seen in normal weight group (374.80 $\pm$ 185.08 ng/L; 12.78 $\pm$ 6.8 pg/ml) respectively, yet the highest number of clinical pregnancy was observed in overweight group (42%).A strong correlation of Kisspeptin with Leptin ($r=0.794$, $P=0.001$) was observed in the overweight females
Conclusion
Leptin-Kisspeptin-fertility link is expressed by maximum number of clinical pregnancies in the female group that showed strongest relationship between serum Leptin and Kisspeptin levels, irrespective of their BMI.

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P363

Effects of myoinositol and D-chiro inositol on hyperandrogenism and ovulation in women with polycystic ovary syndrome: a systematic review

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Background
Insulin resistance is a hallmark of Polycystic Ovary Syndrome (PCOS). Insulin sensitisers, most notably metformin, are thus used to treat the condition, but may be accompanied by gastrointestinal side-effects. The novel isomeric insulin sensitising agents D-chiro-inositol (DCI) and Myo-inositol (MI) improve insulin resistance by acting at the peripheral and ovarian level, respectively, whilst largely being devoid of adverse effects.
Objectives
To assess the efficacy of DCI and MI, alone or combined, on restoration of ovulation and reduction of hyperandrogenism in women with PCOS.
Methods
The following databases were systematically searched: CENTRAL, Ovid-EMBASE, Ovid-Medline, Global health library, SCOPUS and PUBMED. Joint primary outcomes were defined as effect on ovulation and improvement of dermatological manifestations of hyperandrogenism, with effect on serum androgen levels categorised as a secondary outcome.
Results
Eleven trials were deemed suitable for systematic review. Six analysed the effect on ovulation using serum progesterone, luteal ratio or percentage of participants who ovulated. Compared to placebo, MI and DCI led to a rise in mean peak progesterone and an improvement in luteal ratio. Two studies reported a reduction in acne, and hirsutism decreased in all trials with MI treatment. Neither isomer was found to be superior to the other in improving the manifestations of hyperandrogenism. A value of -0.76 for cohen's d measure of effect size (CI -0.17 to -1.35) after 6 months of combined treatment favoured dual isomeric treatment over monoisomeric (MI) treatment for reduction of serum androgen levels.
Conclusion
Myoinositol and D-chiro-inositol both appear to be effective in improving ovulation and reducing hyperandrogenism in women with PCOS. Further randomised controlled trials are needed to establish whether dual isomer therapy offers additional benefits compared to either agent alone.

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P364

Aortic dissection in Turner syndrome: a single centre experience

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Introduction
The risk of aortic dissection (AoD) is significantly increased (40 per 100,000/y) in women with Turner Syndrome (TS), but the clinical profile and management for those at risk are not well-established. To gain a better understanding, we present the experience of a single centre with multidisciplinary care, including dedicated cardiology, for management of TS in adulthood.
Methods
Retrospective case-review of women developing AoD. Cardiac risk factors, echocardiography and cardiac-MRI (CMR) were recorded. Aortic dilatation was defined as ascending aorta diameter indexed to body-surface-area (AAi) $>$ 2.0 cm/m^2.
Results
Three women, all 45,X, suffered fatal AoD, aged 20, 21 and 22-years. All had bicuspid aortic valve, but no evidence of coarctation. All were receiving oestrogen-replacement. Two were hypertensive (one on amlodipine). There was no history of pregnancy. All had AA dilatation:
– Patient A. Echo (5-months prior to AoD): AA 4.0 cm / AAi 2.7 cm/m^2, sinuses 3.3 cm / 2.2 cm/m^2.
– Patient B. Echo: AA 3.5 cm (versus 2.5 cm 1-year before). CMR: AA 3.4 cm / AAi 2.1 cm/m^2, AA/DescendingA ratio $=2.0$.
– Patient C. CMR: AA 4.7 cm (versus 4.4 cm at CMR 1-year before), AA/DescendingA ratio $=2.2$.
Conclusions
1) Mean age of dissection (21-years) was significantly younger than the average age reported in the literature (29-35 years). 2) All were 45,X, had bicuspid aortic valves and dilated AAi, suggesting these are important risk factors. 3) Among the two women with serial scans, excessive AA growth was noted. This is in contrast to a previous report which showed no increased aortic dimensions in 5 women prior to AoD. This emphasizes the importance of screening/follow-up as AoD is a significant cause of premature mortality. Accordingly to the new TS-guidelines, we use baseline-CMR as soon as feasible, and educate all TS women to seek prompt evaluation if symptoms consistent with AoD occur. An AoD-pocket-card is also provided to alert emergency personnel about the higher risk of AoD in TS patients.

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P365

Effects of feed supplementation with olive oil on serum testosterone, triiodothyronine, thyroxine and some biochemical metabolites in Teddy goat bucks

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Teddy is a highly proliferative goat breed, as females of this breed are famous for high twinning rates. Feed supplementation of olive oil has been shown to improve semen quality of goat bucks. In this study, the effects of feed supplementation with olive oil on serum testosterone, triiodothyronine (T3), thyroxine (T4) and some biochemical metabolites in Teddy goat bucks were investigated. For this purpose, 9 adult male goats, with clinically normal reproductive tract, were randomly divided into three equal groups A, B and C. Animals in Group A were fed control ration (control group), while goats in groups B and C were fed ration supplemented with 15 and 30 ml Olive oil, respectively, daily for 8 weeks. Blood samples were collected weekly from each buck and analyzed for serum testosterone, T3 and T4 concentrations through ELISA. Similarly, serum alanine aminotransferase (ALT), Aspartate aminotransferase (AST), total cholesterol, triglycerides and glucose were determined using commercially available kits.
Results revealed that serum concentrations of testosterone, T3 and T4 were higher ($P<0.05$) in bucks of groups B and C compared to those of control group. However, differences in concentrations of these hormones between bucks of the former two groups were non-significant. Among biochemical metabolites, serum ALT, total cholesterol and triglycerides differed significantly among three groups, values being highest in control group and lowest in group C ($P<0.05$).

Serum AST activity was also lower in bucks of groups B and C than control, however, difference between groups B and C was non-significant. Similarly, the treatment had no effect on serum glucose concentrations. Based on results of the present and previous studies, it was concluded that feed supplementation of olive oil improves semen quality and libido of Teddy goat bucks. However, its effects on health biomarkers and fertility rates of buck may be investigated before making any recommendation.

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P366

Audit of endocrine investigations undertaken in females with elevated testosterone

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Background and Aims
Clinical management of women with hyperandrogenic symptoms varies widely and UK guidelines are lacking. Dependent on presentation, differential diagnoses may include thyroid dysfunction, hyperprolactinaemia, congenital adrenal hyperplasia (CAH), hypercortisolism, acromegaly and pregnancy. Women presenting with hyperandrogenic symptoms can have a normal or elevated testosterone. This study describes hormone requesting relevant to these conditions in women with newly elevated testosterone concentrations.
Method
Women, 18-45 years old, with a serum testosterone (TEST) >1.7 nmol/L were identified from laboratory databases for a one year period beginning 01/06/2015. Exclusion criteria were: elevated TEST in previous year, an elevated human chorionic gonadotrophin at baseline; known CAH; or known transgender patient. Follow-up period was 6 months. Frequency of requesting for thyroid stimulating hormone (TSH), prolactin (PRL), 17-hydroxyprogesterone (17OHP), anti-Müllerian hormone (AMH), urine cortisol (UCORT), and insulin-like growth factor 1 (IGF1) were described.
Results
For 368 women, frequency of baseline requesting was as follows: TSH = 73%; PRL = 52%; 17OH*P* = 1.6%; AMH = 22%; IGF1 = 0.5%. Percentage abnormal results (results outside the reference interval or above clinical cut-offs) were: TSH = 8%; PRL = 19%; AMH = 59%. Combined frequencies of tests at baseline and during follow up were: TSH = 78%; PRL = 55%; 17OH*P* = 6%; AMH = 26%; IGF1 = 0.5%; UCORT = 1.1%. Combined frequencies of abnormal results at baseline and during follow up were: TSH = 8%; PRL = 19%; AMH = 59%; UCORT = 25%. TEST requests were repeated in 10% of women, 61% of which remained elevated.
Conclusion
Results show wide variation in the extent of investigation of hyperandrogenism, suggesting variation in knowledge of key diagnostic criteria and the rigour with which differential diagnoses are sought. Additional tests are not often requested in the follow up of an elevated testosterone. An exception is 17OHP, with 8% of subjects tested in the follow-up period, compared with 1% at baseline. Further work is required to correlate requesting patterns with degree of TEST elevation and describe patterns in women with normal baseline TEST.

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P367

Turner syndrome management. Are we going along with the new clinical guidelines?

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Introduction and aim
Turner Syndrome (TS) is associated with a variety of morbidities affecting nearly every body system, and necessitates multidisciplinary management. To facilitate care, the International Turner Syndrome Consensus Group have drafted Clinical Practice Guidelines that were disseminated to ESE members in April 2017. The aim of this audit was to assess whether current management of adolescent and adult TS women in our care is in accordance with the proposed guidelines.
Patients and Methods
TS women were identified from hospital databases, in both Endocrinology and Paediatric and Young Adult Gynaecology Units and data were extracted from their files and compared to the proposed guidelines.
Results
We identified 16 women aged 16-61 years. Their average height and weight was 150 ± 6.87 cm and 58.5 ± 10.01 kg respectively. 6 out of 8 patients with reported data (75%) had been treated with GH treatment before the age of 13, and none had induction of puberty at age 11-12 years. Only 2/16 (12.5%) patients had had a 5-yearly audiometric evaluation and a dental/orthodontic evaluation. 13/16(81%) had performed at least one transthoracic echocardiography or CT/cardiac magnetic resonance scan. 3/15(20%) had an annual assessment of blood pressure and 11/16(69%) had been evaluated by a dual energy x-ray absorptiometry (DXA) scan and a neuropsychological/ behavioral assessment. Thyroid function was annually screened in 7/16(44%) women, HbA1c in 5/16(31%), lipids in 10/16(62.5%) and liver function in 7/16(44%). Serum 25-OH-VitD levels were measured every 2-3 years in 6/16(37.5%), and a screening for coeliac disease antibodies had been performed in 4/16(25%) of patients.
Conclusion
A significant proportion of TS women may miss health checks proposed by the International TS Consensus Group. This highlights the need for a better care plan strategy so as to engage and motivate these women for lifelong follow up in order to optimize their quality of life and reduce their comorbidities.

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P368

Polycystic Ovarian Syndrome (PCOS): Social situation influences Cardiometabolic Outcome

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Introduction
Previous studies have shown that PCOS (first described 1935) increases the future risk of hypertension and coronary artery disease.
Aims
We investigated in women with PCOS, the link between social disadvantage and markers of cardiometabolic risk and how weight gain over time related to social disadvantage.
Methods
In a primary care-based study, 1797 women were identified from patients attending one of 40/42 GP practices located in Central/Eastern Cheshire and Derbyshire, UK. The search was performed with the assistance of the EMISWeb® database.
Results
Descriptive: Mean age of the 1797 women at diagnosis with PCOS/PCO was 24.6 (standard deviation 6.5) years (age range 11-69 years). Of group studied, 46.1% of women had a BMI of 30 or more. 1646 out of 1797 (91.6%) had at least one BMI measurement and 1726 (96.0%) had at least one blood pressure check over the follow-up period.
Relation of BMI, SHBG and glucose level to social disadvantage: A higher BMI (closest BMI to diagnosis date with PCOS) associated with a higher Townsend index (indicative of higher social disadvantage) ($r^2 = 0.04$; $P = 0.005$) as did lower SHBG ($r^2 = 0.013$; $P = 0.009$). This relation held when adjustment was made for age, BMI, and systolic BP. There was no relation of fasting glucose/random glucose with Townsend Index.
BMI trends over time: BMI increased more in women with a higher Townsend Index. Specifically for the most disadvantaged women, BMI increase (latest compared with earliest recorded BMI) was 18.6% compared with the most advantaged quintile at 13.7%.

Conclusion
Higher BMI and lower SHBG levels in women with PCOS were associated with greater socioeconomic disadvantage. The greater increase of BMI in more socially disadvantaged women suggests that socioeconomic situation influences obesity risk in PCOS women. The corollary is that measures that reduce inequality may impact on longer term cardiometabolic outcome in PCOS women

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P369

Polycystic Ovarian Syndrome: Assessment of approaches to diagnosis and cardiometabolic monitoring in UK primary care

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Introduction
Polycystic ovarian syndrome (PCOS) is one of the commonest endocrine disorders affecting women of reproductive age. We examined the specific tests that are done in primary care to lead to the diagnosis of PCOS, and to support the diagnosis once made.
Methods
1797 women were identified from a pooled GP practice database. The search included all patients defined with PCOS or related terms. Records included demographic information, medical history (diagnoses), blood test results and whether a pelvic ultrasound scan had been performed.
Results
The most commonly age of PCOS diagnosis was 20-29 years. 67.7% of the women had at least one concomitant Read coded diagnosis. Most pelvic ultrasound scans were performed in the month immediately prior to diagnosis. In the 12 months prior to the diagnosis of PCOS being made, 30.5% of women underwent a measurement of their serum total testosterone level while 29.6% had their serum SHBG measured. For serum oestradiol the corresponding statistics were 28.4%, LH 45.3% and for FSH 45.5% checked before diagnosis. Fasting blood glucose, random glucose and HbA1c were checked in 10.2%, 18.8% and 4.2%, of women before diagnosis respectively, but in only 7.9%, 6.0% and 3.4% of women in the 24 months after diagnosis. There was a tendency for endocrine testing (oestradiol, LH, FSH, testosterone, SHBG) to peak in the weeks before diagnosis. For plasma glucose, testing was performed more evenly over time as for serum cholesterol. Of all women diagnosed with PCOS, 32.8% were prescribed metformin, 3.7% antihypertensives, 2.2% statins and 63.5% an oestrogen containing contraceptive pill or HRT.
Conclusion
The underlying pathophysiology of PCOS is still not fully understood. As a result, treatment is often focused on individual symptoms, not the syndrome itself. Robust laboratory led protocols would provide the necessary information to enable an appropriate diagnostic evaluation / cardometabolic monitoring.

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High prevalence of multimorbidity in overweight and obese women with Polycystic Ovary Syndrome (PCOS)

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Background
Multimorbidity, presence of 2 or more chronic conditions, is a growing issue for patients as well as health systems. Reported prevalence of multimorbidity in females in a UK study was 23%. Presence of an additional chronic condition adds challenges to an existing condition. The difficulties of living with polycystic ovary syndrome (PCOS) have been well described both in terms of dealing with the symptoms as well as the potential metabolic and mental health issues associated with this condition. Reports of multimorbidity are scarce in women with PCOS.
Methods
Post-hoc analysis of a lifestyle intervention study data ($n = 161$) in overweight or obese women (Body Mass Index (BMI) ≥ 23 kg/m^2 for Black and Minority Ethnicities and BMI ≥ 25 kg/m^2 for White Europeans) aged 18 to 49 years with a diagnosis of PCOS. Patients with a confirmed diagnosis of diabetes were excluded from the lifestyle intervention study. Multimorbidity was defined as presence of at least one chronic condition other than PCOS reported by patients and corroborated by their medication list, or clinical measurements.
Results
82 (51%) of 161 women (mean age 33.4, 69% white) had multimorbidity (58 white); 49 (one other chronic condition), 21 (two other chronic conditions) and 12 more than two. The most common conditions were; Asthma (34, 21%), Depression (24, 15%), Hypothyroidism (15, 9%) and Hypertension (13, 8%). Other recorded conditions (47 altogether) were: Epilepsy, Menieres' diseases, chronic pain, irritable or inflammatory bowel diseases, Uveitis, Congenital Cardiomyopathy, Migraine, Multiple sclerosis, psoriatic arthritis, endometriosis.
Conclusion
The prevalence of multimorbidity in this young cohort of overweight and obese women with PCOS is high. Living with multiple chronic conditions and using multiple medications are added challenges and need to be considered when addressing their PCOS treatment.

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Standardisation of care: a quality improvement project in Polycystic Ovary Syndrome (PCOS) clinic

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Background
Considering the high prevalence of metabolic and mental health issues associated with PCOS, it is important to screen for these routinely in clinic. We aimed to implement a standard approach to ensure we do this in our specialist PCOS clinic.
Methods
We introduced a standard 'PCOS clinic pack' which included the following documents and data collected for analysis
1. Checklist for doctors to ensure the long term health consequences of PCOS (metabolic and mental health) are discussed with patients.
2. Introductory letter on arrival at reception to inform patients about the process, with space to document the subjects they wished to discuss with their physician.
3. Epworth Sleep Apnoea questionnaire
4. Modified Ferriman-Gallway self-scoring form.

Results
124 women with PCOS, mean age 32 years, attended the speciality clinic between January and April 2017. 88 (70%) of the packs were returned and not all data sets were complete. 57 patients had documented their agenda, which could be broadly categorised into 'explanatory / reassurance' and 'treatment' related concerns about their PCOS. Example questions were
"*What can I do about my….* ": hair, weight, irregular periods OR
"Can you explain…": "*what is PCOS*", "*My fertility chances*" and "*my treatment options*".
Conclusion
A systematic check-list approach has been shown to be successful in other endocrine conditions such as Turner's syndrome. During a routine clinic, there is a risk that important aspects of PCOS may be missed both from the doctor and patient perspective. We aim to refine our 'PCOS clinic pack' further to capture and present more data in the future, and have started education groups to ensure patients with PCOS' agendas are fully met.

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A rare case of Gestational Hyperandrogenism

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A 27 years old primigravida, with no significant past medical history, was referred to Endocrine clinic at 37 weeks gestation with hirsutism. She developed hirsute features during pregnancy and symptoms progressed with advancing gestation. Her physical examination revealed thick coarse dark hair growth in the midline of lower abdomen, between the breasts and forearms. She noted deepening of her voice but denied headaches, visual disturbance or clitromegaly.
A hormonal profile at 37 weeks gestation showed very high serum testosterone level at 37.9 nmol/L, raised androstenedione >35 nmol/L with normal DHEAS at 1.6 μmol/L and suppressed FSH and LH at
The hormonal profile returned back to normal with normal testosterone and androstenedione after delivery and has remained normal on repeating the hormones. The female baby did not showed any evidence of virilisation.
The patient represents a very rare condition of high testosterone in pregnancy returning back to normal following delivery and there are a few cases in the literature. This condition most frequently arises in the third trimester, virilisation of the mother occurs in a third of cases. Virilisation of the foetus has not been reported. The exact pathological mechanism of this condition is not known, differential diagnoses include pregnancy luteoma and Theca-lutein cysts. As our patient was primigravida, caucasian and had polycystic ovaries, the likely diagnosis is Theca-lutein cysts.

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P373

Successful stimulation of spermatogenesis in a man with hypogonadotrophic hypogonadism, azoospermia, previous right orchidectomy and a remaining small left testicle

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Introduction
Infertility affects 15% of couples and a male factor accounts for 50% of cases. Adequate history taking, examination of both partners, hormone testing and semen analysis are required to ascertain a cause and treatment strategy. Gonadotropin therapy with Human Chorionic Gonadotropin (HCG) and recombinant Follicle Stimulating Hormone (rFSH) is indicated for use in men with reduced spermatogenesis due to hypogonadotropic hypogonadism (HH). We present a man with hypogonadotropic hypogonadism, azoospermia and previous right orchidectomy who received gonadotropin therapy with subsequent stimulation of spermatogenesis.
Case
A 40 year old man presented to the endocrine department in August 2015 with a 4-year history of tiredness, reduced libido and infertility. He was seen by the urologist in 2011 for right undescended testis and had an orchidectomy in January 2015. In March 2014 he attended the fertility clinic and was found to have HH with azoospermia (repeat tests in 2015 and 2016 confirmed the same). An ultrasound revealed a small, well-perfused left testicle of 13 ml-size. His pituitary gland imaging was normal. We commenced subcutaneous HCG 1500 IU three times a week until serum testosterone levels normalised. At month-3 subcutaneous rFSH 150 IU three times a week was commenced while the HCG dose was reduced to 1500 IU once a week. Semen analysis at month-6 and month-9 has revealed progressive improvement in spermatogenesis (concentration, motility, and progressiveness). Three-monthly assessment of testosterone levels, full blood count, prostate specific antigen and liver function tests have been normal. Combined therapy is being continued until appreciable levels of spermatogenesis have been achieved for non-assisted conception and/or for semen freezing and assisted conception treatment.
Conclusion
In conclusion, we describe a man with hypogonadotropic hypogonadism, azoospermia, previous right orchidectomy and a remaining small left testicle, who is currently receiving gonadotropin therapy with subsequent stimulation of adequate spermatogenesis.

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Clinical and biochemical evaluation of a 32 year old patient with hypogonadism.

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A 32 year old emirati patient is evaluated in the endocrine clinic because of symptoms of hypogonadism in the form of reduced sexual desire and erectile dysfunction. On further history taking he confenssed that he was abusing anabolic steroids over the last 3 years but has stopped 3 months prior to his evaluation. On physical exam he appears musculinized, his BMI is 27 kg/m^2. He has acne on his face. Testicular size is around 15 ml bilateral. Has normal hair distribution on his body. Lab tests confirmed the diagnosis of hypogonadotrpoic hypogonadism on the account of two low serum testosterone levels 4.6 and 5.1 nmol/l measured after overnight fast early morning and low LH and FSH below 2 IU/ml. Evaluation of other anterior pituitray hormones showed having mild hyperprolactinemia but the rest were entirely normal. He underwent brain imaging in the form of pituitary MRI which shows that he is having partial empty sella. After discussion with te patient he agrees to take clomiphene citrate and after 6 months of therapy I was able to stop the medicine and his anterior pituitary hormones and testosterone returns back to normal. He is advised to stop abusing anabolic steroids and after another 6 months he is evaluted agin and he is fine his testosterone level is normal.

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Thyroid

P381

Genetic variants modify susceptibility to AF in patients on thyroid hormone replacement therapy

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Purpose
Hypothyroidism has been associated with atrial fibrillation (AF) in some studies. This study aimed to characterize thyroid related genetic variants that may change susceptibility to AF in patients on thyroid hormone replacement therapy (levothyroxine).
Methods
A case-control study was done among patients of European Caucasian ethnicity from the Genetics of Diabetes Audit and Research Tayside (GoDARTS) recruited in Tayside (Scotland, UK). Electronic medical records (biochemistry, prescribing, hospital admissions and demographics) were used to ascertain patients with atrial fibrillation and their controls as well as patients with hypothyroidism, and linked to genetic biobank data. Genetic tests of association were performed by means of logistic regression models adjusted for age, gender and average thyroid-stimulating hormone.
Results
We analysed 1,031 cases of AF and 10,757 controls. Loci on chromosomes 3 (Thyroid Hormone Receptor Beta-THRβ), 6 (human leukocyte antigen-HLA), and 14 (Thyroid Stimulating Hormone Receptor- TSHR) were associated to AF in patients on levothyroxine. A significant interaction between HLA-rs2517532 and levothyroxine use was found (OR = 1.32, 95%CI: 1.03–1.67, $P = 2.6e{-}02$). A significant interaction was also found between TSHR-2234919 and levothyroxine use (OR = 0.48, 95%CI: 0.24–0.97, $P = 4.2e{-}02$). Fifteen unlinked single-nucleotide polymorphisms (SNPs) located on chromosome 3 at THRβ showed interactions with similar size effect estimates (OR = 1.3–1.5, $P < 5e{-}02$), and two SNPs at THRβ (rs7652234 and rs826219) showed larger size estimates (OR = 1.9–2.0, $P < 2e{-}02$).
Conclusions
This study provides evidence that genetic factors, such as polymorphisms in the THRβ, HLA, and TSHR genes, might contribute to inter-individual variations in susceptibility to AF in patients on levothyroxine.

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P382

A population-based study of the Epidemiology of Chronic Hypoparathyroidism

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Aim
We aimed to undertake a population-based approach to describing the prevalence and incidence of chronic hypoparathyroidism. There are very few reports on the epidemiology of this condition.
Methods
Data linkage of all biochemistry, hospital admissions, prescribing and death records was undertaken in Tayside Scotland (population 400,000) from 1988 to 2015. Patients with at least 3 serum calcium concentrations below the reference range from an out-patient setting and who fulfilled at least one of these criteria; had either previous neck surgery/irradiation, a low serum PTH or treatment with Vitamin D were included in the study. Patients with prior severe chronic kidney disease were excluded. Patients were subcategorised into either those with a surgical or a non-surgical cause, and patients with secondary hypoparathyroidism e.g. hypomagnesaemia, were identified.
Results
Overall 18,955 patients with hypocalcaemia were identified of whom 222 patients were identified with primary hypoparathyroidism, 116 with post-surgical and 106 with non-surgical hypoparathyroidism. The prevalence of primary hypoparathyroidism was 40 per 100,000 of the population in 2015. Post surgical and non-surgical rates were 23 and 17 per 100,000 respectively, with 80% of the former and 64% of the latter being female. The annual incidence varied from 1–4 100,000 with a mean serum calcium at diagnosis being 1.82 mmol/l (SD $\pm$ 0.24). Activated Vitamin D was used in 48% of post-surgical cases and 43% of non-surgical cases with 71% all patients being prescribed calcium and/or standard Vitamin D. Over 90% of post-surgical and 64% of nonsurgical cases were prescribed thyroxine and/or hydrocortisone.
Conclusions
Using a population-based approach we identified a large number of patients with non-surgical hypoparathyroidism, many with mild hypocalcaemia not requiring treatment. Two thirds of these patients were on hydrocortisone and/or thyroxine suggesting an autoimmune aetiology.

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Novel driver mutations in thyroid cancer recurrence

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Worldwide, ~300,000 new cases of differentiated thyroid cancer are reported per annum and thyroid cancer now represents the most rapidly increasing cancer in the US and in the UK. In general terms, outcome is good (10-year survival $>$90%). However, up to 25% of patients develop local or regional recurrences, and have a significantly reduced life expectancy. We hypothesise those thyroid tumours which subsequently recur display a distinct pattern of driver mutations, and that molecular characterisation of these mutations will reveal novel mechanisms involved in thyroid tumour recurrence. Next generation sequencing was performed and whole genome sequencing data downloaded from The Cancer Genome Atlas (TCGA), prior to filtering and bioinformatic analysis. This identified mutations in a number of biologically significant 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), which occurred in tumours which subsequently recurred. As in silico analysis suggested all variants to be potentially pathogenic, expression vectors were obtained for each gene and site directed mutagenesis performed to recapitulate the mutations. Subcellular localisation, proliferation, cellular migration and invasion were all investigated in cell lines which represented the background driver mutation of each tumour (TPC1: RET/PTC; SW1736: BRAF; Cal62: KRas). In TPC1 cells IMPDH2 and DICER1 mutations induced significantly increased cell migration at 24 hours, and overexpression of IMPDH2 resulted in altered intracellular localisation into intracellular discrete bodies. Our on-going studies show mutated genes demonstrating some aspects of the aggressive phenotypes that would be expected to be associated with tumour recurrence. However, there are clearly different mechanisms by which these mutations are functionally pathogenic, and modelling tumour recurrence is particularly challenging. For these mutations in IMPDH2, PFKFB4 and DICER1 in silico prediction of pathogeneity is not enough to understand the complexity of tumour mutation interactions, confirming the necessity of concomitant in vitro analysis.

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Urinary Iodine to Creatinine ratio (UI/C) during pregnancy is not associated with adverse obstetric outcomes

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Background
Maternal severe iodine deficiency has been associated with pregnancy and neonatal loss but the impact of mild-moderate iodine deficiency on pregnancy is not well-documented. Mild-moderate iodine deficiency during pregnancy is common even in iodine replete countries. In the UK women of reproductive age have been found to be mildly-to-moderately iodine deficient. UI/C is an optimal indicator for iodine status in pregnancy.
Aims
We investigated whether insufficient iodine status during pregnancy is associated with adverse obstetric outcomes defined as pregnancy or child loss by age 1 year or obstetric complications including pre-eclampsia, hypertensive disorders of pregnancy, glycosuria, anaemia, caesarean delivery, malpresentation, low/high birth weight percentiles, pre-term delivery, antepartum and post-partum haemorrhage.
Methods
We analysed outcomes of 3182 singleton pregnancies from the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort. Mother-child pairs were selected based on availability of UI/C measurements. First, we compared UI/C in mothers with babies alive at 1 year to those with pregnancy/child loss (n=42). Next, we analysed the relationship between UI/C and pregnancy outcomes in 3140 pairs with live babies. We compared the incidence of outcomes in four UI/C categories: $<$50.0; 50–149; 150–250; 250+ μg/g. Additionally, we compared the UI/C as a continuous variable in those with and without a complication of interest.
Results
The median urinary iodine concentration in the entire cohort was 92.25 μg/L (classed as iodine insufficient) and the median UI/C 123.9 μg/L. There were no relevant demographic differences between the mothers with live babies and those who suffered loss. There were no statistically significant differences in median values of UI/C between the two groups. The incidence of studied outcomes did not differ among the four UI/C categories, nor were there any statistically significant differences in the median UI/C when stratified based on the studied outcomes.
Conclusion
Iodine-to-creatinine ratio was not associated with significantly different obstetric outcomes in an iodine-insufficient pregnant population.

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P385

Marked increases in levothyroxine prescribing and laboratory testing following a reduction in the upper end of the TSH reference range

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Context
Subclinical hypothyroidism is a common clinical problem defined as an elevation in serum thyrotrophin (TSH) with normal circulating free thyroid hormone levels. Empiric treatment of mild subclinical hypothyroidism (mSCH) is controversial.
Objective
To evaluate the change in the levothyroxine prescribing rate and TSH testing following a decrease in the TSH reference range from 6 to 4 mU/L in a large urban center.
Design, Setting, Patients, Outcome Measures
With 45,000–65,000 TSH tests performed per month, we were able to build a very robust model to accurately predict the volume of TSH tests and compare this to actual TSH test volumes before and after the reference range change. We also evaluated the dispensation rate of new levothyroxine prescriptions and new levothyroxine dosage increases before and after the change.
Results
Prior to the TSH reference range change, the actual and predicted TSH volumes per month followed an almost superimposable pattern. After the change, a persistent separation emerges with actual TSH test volumes exceeding those predicted by 7.3%. Patients labelled with mSCH almost tripled, from 3.3% to 9.1%. New levothyroxine prescriptions increased by 25.3% from 2013 to 2014 ($P<0.001$). For pre-existing levothyroxine users, there was a significant increase in dose escalation ($P<0.001$).
Conclusions
Clinicians may rely heavily on TSH to make decisions about levothyroxine prescribing and dosage change even with only modestly elevated results. We speculate there may be a knowledge care gap regarding the lack of strong evidence supporting the treatment of mSCH.

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Prevalence of and factors predicting thyroid dysfunction at the time of ST- and non-ST- elevation myocardial infarction – the ThyrAMI 1 study

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Introduction
Thyroid dysfunction is common affecting 5–10% of the adult population. Cardiovascular disease, including acute myocardial infarction (AMI), has been suggested as one of the adverse outcomes of thyroid disease. Furthermore, individuals with thyroid dysfunction at the time of AMI have worse outcomes. Despite this, there is scarce data on the prevalence of thyroid dysfunction in patients with AMI. We conducted a prospective observational multi-centre study to investigate the prevalence of and factors predicting thyroid dysfunction in patients with AMI.
Methods
Consecutive patients ($n=1970$) from five hospitals within the North-East of England with AMI (both STEMI and NSTEMI) between January 2015 and December 2016 were recruited. Thyroid function tests were evaluated on the first available sample between 1–24 hours of admission. Patients on medications affecting thyroid function were excluded from the analysis. The prevalence of thyroid dysfunction was calculated and logistic regression analysis performed to assess relationship with demographic, clinical and biochemical variables.
Results
The thyroid status of the 1809 patients were: 78.6% ($n=1422$) euthyroid, 17.3% ($n=314$) subclinical hypothyroidism (SCH), 1.2% subclinical hyperthyroidism, 2.7% ($n=49$) low T3 syndrome (LT3S), and overt hypothyroidism and hyperthyroidism 0.5% each. Predictors for SCH were increasing age with OR (Odds ratio (95% CI) of 1.02 (1.01–1.04); $P=0.001$, STEMI with OR 2.11 (1.52–2.93); P
Conclusion
Thyroid dysfunction is common in patients presenting with AMI particularly SCH that is present in 1 in 6. Furthermore, troponin rise is higher in SCH patients with AMI, independent of other factors, which may partly explain the increased morbidity and mortality observed in these patients. Interventional studies are necessary to evaluate if treatment post-AMI improves outcomes.

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The Oxford Multidisciplinary Thyroid Eye Disease Clinic: Can short waiting times and use of Steroid Sparing Agents reduce total glucocorticoid dose and requirement for surgery/radiotherapy?

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Introduction
The Oxford multidisciplinary thyroid eye disease (TED) clinic comprising an oculoplastic surgeon, rheumatologist and endocrinologist with access to orthoptics, neuroradiology and radiotherapy was established in 2013. The aim of the service is to facilitate rapid referral and treatment in a specialist centre in keeping with the Amsterdam Declaration. Early use of steroid sparing agents (SSA) and recently rituximab form part of the treatment regimen.
Methods
A retrospective, 4-year, single-centre, consecutive case series of patients with TED audited outcome using the VISA classification and treatment modalities, at presentation and 1 year follow-up.
Results
111 patient records were analysed. Mean wait from referral to first review was 1 month with 35.1% of referrals originating from endocrinology departments. Mean age was 51.2 years (10–84). 25.2% ($n=28$) of patients were male and 34% were current/ex-smokers. Where thyroid biochemistry was available at referral ($n=86$): 53% were euthyroid, 43% hyperthyroid and 4% hypothyroid. TSHRAb was positive in 84% of patients checked compared to 62% of TPO Ab. Presenting signs included: ocular surface disease (69%), exophthalmos (53%), diplopia (45%), eyelid retraction (35%) and reduced vision (9%). Presenting activity was mild (VISA $\leq 3/10$) in 60% and severe in 21% (≥ 7); severity mild in 43% and severe in 22%. 1 year data ($n=36$) showed mild activity at 1 year in 95% (38.9% at referral) and 0% severe disease (33% at referral). Intravenous methylprednisolone was administered to 33 patients; 42% received ≤ 1.5 g total with use of SSAs: methotrexate ($n=31$), azathioprine ($n=6$), ciclosporin ($n=10$) and Rituximab ($n=9$). Orbital decompression surgery was performed in 12.6% ($n=14$), squint surgery 12%, eyelid surgery 22% and orbital radiotherapy 6%.
Conclusion
Early use of SSAs has significantly reduced the overall steroid load in patients when compared to established European guidance (EUGOGO). This regimen confers a low orbital decompression and orbital radiotherapy rate.

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P388

An electronic protocol replicating QOF thyroid alerts improves monitoring but does not help optimise levothyroxine replacement in hypothyroidism in primary care

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Introduction
Thyroid quality indicators were removed from the Quality Outcome Framework (QOF) targets in 2014, resulting in discontinuation of statutory system alerts to remind GPs to check annual thyroid function in patients with primary hypothyroidism treated with levothyroxine.
Aim
To investigate the impact of the discontinuation and reinstitution of the QOF thyroid e-alerts on the management of hypothyroidism in primary care.
Methods
Following exclusion of hypothyroidism from QOF indicators in 2014, we developed an electronic protocol in Emis Web to emulate the QOF thyroid e-alerts. We piloted these alerts in a single Surrey GP practice (patient population 8057, $n=257$ with treated hypothyroidism). In 2016, we audited, in the population meeting the QOF criteria for inclusion in the thyroid register (Thy001), the percentage of patients who 1) had had TSH checked in the preceding 12 months (Thy002) and (2) had latest TSH level within the local laboratory reference range of 0.35–5.0 mU/L. We compared standards in the pilot

practice with those in 4 control practices without alerts (total population 63,534 [range 7070–33,314]; $n=1953$ with treated hypothyroidism).
Results
During the period of statutory hypothyroidism alerts (2009–2014), 98–100% of patients with hypothyroidism in both pilot and control practices met QOF Thy002 requirement. Following removal of hypothyroidism from QOF, 90% of hypothyroid patients in the pilot practice with electronic alerts had a 12-month TSH check compared with 77% in control practices without alerts. However, the proportion of patients with TSH within the reference range was similar in pilot and control practices (67% vs. 69%).
Conclusion
The removal of hypothyroidism from the QOF targets has been associated with deterioration in TSH monitoring in primary care. An electronic protocol replicating QOF Thy002 alerts improves thyroid monitoring but not biochemical control of hypothyroidism. An e-protocol to prompt action when TSH is outside the reference range in patients with treated hypothyroidism has been developed and is currently being piloted.

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Morbidity and Mortality in patients with Chronic Hypoparathyroidism

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Aim
We aimed to investigate mortality and morbidity in patients who were identified with primary hypoparathyroidism, post-surgical and non-surgical hypoparathyroidism.
Methods
The patients who were previously identified with hypoparathyroidism, were linked to hospital admission dataset, renal registry, biochemistry dataset and prescribing dataset. In this study, death and 6 morbidities; cataract, circulatory system, infection, fracture, mental health disorders and eGFR were identified through OPCS and ICD codes. The percentage of each outcome after diagnosis of hypoparathyroidism were compared between post-surgical and non-surgical hypoparathyroidism groups. Patients were separated into two age groups; <60 and $ 60 years old for this analysis. The mean and median duration from time of diagnosis to outcome were measured. Chi-squared test was used to compare the percentage of each event between the two groups.
Results
There were 222 patients who were previously identified with primary hypoparathyroidism, 116 with post-surgical and 106 with non-surgical hypoparathyroidism. The mean age of the patients was 48.7 years (SD: 19.0) and 72.5% of patients were female. The mean duration of follow-up from time of diagnosis till end of study was 14.7 years (SD: 8.8). The overall rates of death, circulatory disease and mental health disorders among these patients were 28.4%, 32.0% and 51.8% respectively. In patients who were below 60 years old, there were significantly higher percentage of circulatory disease ($P=0.024$) and death ($P=0.019$) in the non-surgical hypoparathyroidism group compared to the post-surgical group. However, in patients who were 60 and above, there were significantly higher percentage of death ($P=0.012$) and eGFR lesser than 30 ml/min/1.73 m^2 ($P=0.001$) in the non-surgical group.
Conclusion
Patients with hypoparathyroidism had high rates of circulatory disease, mental health disorders and death. Circulatory diseases, renal failure and death were more common in non-surgical hypoparathyroidism than in post-surgical hypoparathyroidism.

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P390

Thyrotrophin receptor antibodies (TRAb) and other autoantibodies after treatment of Graves' disease

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Introduction
Following treatment of Graves' disease (GD), levels of thyrotropin receptor autoantibodies (TRAb) tend to decrease depending on treatment modality and length of follow up. We have assessed TRAb biological activity at follow up, years after GD treatment.
Subjects and methods
TRAb concentration and biological activity were measured in 69 GD patients (59 females; 10 males; median age 59 years; TRAb positive at diagnosis), with follow up ranging from 1 to 13 years. Sera were also tested for TgAb, TPOAb and GADAb.
Results
31/69 (45%) GD patients remained positive for TRAb one or more years after diagnosis. Fifteen of these were TRAb positive for longer than 5 years after diagnosis. Of the TRAb positive patients 21/31 (68%) were positive for stimulating TRAb (TSAb; range $=155$–3894% stimulation). One TRAb positive patient was positive for blocking type TRAb (TBAb) (42% inhibition). Mean TRAb levels decreased between diagnosis and at follow up irrespective of treatment group – (a) Carbimazole (CBZ; $n=26$) 7.1 U/L vs. 3.1 U/L; (b) radioiodine (RAI; $n=26$) 11.9 U/L vs 6 U/L; (c) surgery ($n=13$) 20.7 U/L vs. 2.4 U/l; (all $P<0.01$). Serum TRAb increased at follow up in 3/26 (CBZ) and 4/26 (RAI) patients. There was good correlation between TRAb and TSAb ($r=0.82$; $n=30$).

Autoantibodies at follow up	TRAb + ve ($n=31$)
Follow up – median (range)	5 years (1-13)
TSAb positive	21/31 (68%)
TBAb positive	1/31 (3%)
TPOAb, TgAb, GADAb positive respectively	25/31, 18/31, 3/31 (81%, 58%, 10%)

Discussion
In this cohort of GD patients: (a) TRAb concentrations decreased following treatment; (b) some patients remained TRAb positive for 5 or more years after diagnosis; (c) two thirds of TRAb positive subjects had detectable TSAb at follow up (d) some also remained positive for TPOAb and/or TgAb at follow up; and (e) GAD Ab were detectable in 10% at follow up.

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P391

Iodine status on the Island of Ireland

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Iodine is a trace element required for thyroid hormone production. Requirements increase in pregnancy, when even mild deficiency may affect offspring neurocognitive development.
The gold standard for assessing iodine status is population surveys of urinary iodine concentration (UIC). The WHO also suggests a population prevalence of $>3\%$ of TSH values >5 mIU/L indicates deficiency. A recent UK survey of 700 teenage girls demonstrated mild iodine deficiency (median UIC 80 μg/L; sufficiency >100) with seasonal variation. We recently demonstrated iodine deficiency in 240 pregnant women in Belfast associated with poor dairy intake.
We surveyed 903 girls aged 14–15 years in seven sites across Ireland with spot urine collections and iodine specific food frequency questionnaires. We also sampled a range of milk available for sale at each site bimonthly including organic brands. The median urinary iodine concentration (UIC) was 111μg/L. All areas were sufficient except Galway (98μg/L). A positive correlation was found between UIC and milk consumption estimated from ($P<0.001$). In the two sample sites surveyed twice UIC levels were lower in summer vs winter months ($P=0.005$).

Milk samples collected from Galway and Roscommon had a lower mean iodine concentration compared to those from Derry/Londonderry ($P<0.05$). Organic milk had similar levels to nonorganic milk.
Neonatal blood spot TSH results of all 354,403 infants born in NI between 2000–2014 were also reviewed and 0.5% of neonates had a TSH > 5 mIU/L. Higher TSH levels were found in babies born during summer months.
These analyses suggest iodine sufficiency in Ireland, although of borderline degree. Altered eating habits in pregnancy, along with seasonal and geographical factors may combine to increase the risk of iodine deficiency. Continued population monitoring and pre-pregnancy education is required in the British Isles while there remains no iodine fortification program.

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P392

The relationship between free T4 and thyrotropin receptor antibodies is log-linear and negatively influenced by age and smoking in patients with Graves' disease

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Background
The third generation thyrotropin receptor antibodies (TRAb) assay has high sensitivity and specificity in diagnosing Graves' disease (GD). Circulating levels of TRAbs predict the disease course of Graves' orbitopathy (GO) and remission rates in GD. However, the relationship between TRAb and thyroxine (FT4) and the factors affecting their interaction are unclear.
Method
A prospective cohort study was conducted to evaluate the relationship between TRAbs and free thyroid hormones, as well as to assess the impact of other factors on this relationship. The diagnosis of GD was confirmed in patients with hyperthyroidism by the presence of raised TRAb levels and/or uniform uptake on Technetium scan. The clinical and biochemical information was collated at diagnosis prior to commencement of antithyroid drug therapy. The baseline free thyroid hormones were correlated with TRAbs using linear regression models, which were adjusted for gender, age, coexisting GO and smoking status.
Results
A total of 370 consecutive patients with Graves' hyperthyroidism were studied. The mean age (SD) of the patients was 47.6 (15) years and most was females (85%). Serum FT4 levels showed a log-linear relationship with TRAb levels at diagnosis (adjusted $R^2=0.25$). The relationship between TRAb and FT4 was negatively and significantly influenced by age (older patients produced approximately half the serum FT4 concentrations in response to similar TRAb levels than younger ones) and smoking. Conversely, the presence of GO was positively associated with higher serum FT4 levels, independent of TRAb concentrations.
Conclusion
Our data demonstrates a log linear relationship between TRAb and serum FT4 concentrations. Furthermore, aging and smoking are associated with decreased thyrocyte responsiveness to TRAb modulation. Future studies to assess stimulatory and blocking TRAb components may help to provide a mechanistic explanation for this observation. Meanwhile, our data provides useful information for clinicians to help inform treatment decision in managing GD.

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P393

Long-term relapse rates following thionamide withdrawal in Graves' thyrotoxicosis and the predictive role of TRAbs

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Background
Thionamides are a safe and effective treatment for Graves' thyrotoxicosis and tend to be favoured over radioiodine in the UK. Risk of recurrence following cessation of thionamides is high although most studies tend to have short duration of follow up. We have previously published follow-up data to 4 years in this cohort and now present follow-up out to 7 years.
Methods
Retrospective review of first presentation Graves' disease where a course of thionamide was completed ($n=282$). Age, gender, smoking status, free T4, total T3, TRAb at diagnosis, TRAb at cessation of thionamide and time to normalization of thyroid function were assessed.
Results
Recurrent thyrotoxicosis occurred in 30% (84/282) at 1 year, 41% (113/273) at 2 years, 50% (130/259) at 3 years, 56% at 4 years (127/228), 62% at 5 years (101/163), 59% at 6 years (66/111) and 65% at 7 years (58/89). Logistic regression identified younger age and higher TRAb at cessation, as independent predictors of recurrence. 1 year after thionamide withdrawal, cessation TRAb <0.9 mU/L was associated with a 22% risk of recurrence compared to 46% when TRAb was ≥1.5 mU/L ($P<0.001$). The corresponding figures for 5-year recurrence risk were 54% and 73%, respectively ($P<0.05$). TRAb at diagnosis >12 mU/L was associated with a 79% risk of recurrence over 5 years compared to 47% when diagnosis TRAbs were < 5 mU/L ($P=0.005$).
Conclusions
This cohort provides the longest, well-characterised follow-up of a large number of patients with Graves' disease after planned thionamide withdrawal. High TRAbs at diagnosis, and also at cessation of therapy, are indicative of a very high risk of recurrence. Only one-third of all patients will remain euthyroid in the long-term. In patients where recurrent thyrotoxicosis would be particularly hazardous, early consideration should be given to primary radioiodine therapy.

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P394

Investigating the utility of diffusion weighted magnetic resonance Imaging as an adjunct to clinical assessment in Graves' Orbitopathy (GO)

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Purpose
Early diagnosis and treatment of Graves' orbitopathy (GO) are essential to prevent physical and psychological burdens of advanced disease. MRI diffusion weighted imaging (DWI) is an emerging modality to assist with timely diagnosis. We investigated the value of DWI in early diagnosis and monitoring and its relationship with the clinical activity score (CAS) and quality of life (QoL) scores in a joint endocrine/ophthalmology clinic.
Methods
Ninety-one patients were referred to the clinic between 2011 to 2016. Forty-seven had clinical indices of orbital involvement and underwent MRI DWI imaging. Of these, 20 patients had at least one further scan during the course of the disease. The apparent diffusion coefficient (ADC) was calculated for the most affected muscle on each DWI scan and correlated with CAS and QoL outcome measures (GO-Qol, TED-QoL).
Main Results
Thirteen patients received intravenous methylpredisolone, 5/20 completed orbital radiotherapy and 3/20 had an orbital decompression during monitoring. The most active muscle at presentation was the right inferior rectus ($n=7$, 35%).
Mean CAS at presentation was 2.3/7, followed by CAS 1.2, 0.8 and 0.0 at scan 2, 3 & 4 respectively. Mean ADC value fell over the disease course during treatment from 1120.5 to 766.5. A positive correlation was found between initial CAS and ADC ($r=0.45$, $P=0.04$). All patients who did not subsequently develop significant disease had ADC values <1000 (mean 674.7) at baseline.
Conclusions
We present novel data demonstrating correlation between DWI, CAS and QoL. This may offer predictive benefit that DWI is elevated prior to other disease parameters so may help target patients at high risk of developing severe GO. DWI may serve a valuable adjunct in early diagnosis and monitoring with potential to identify low risk groups whereby low CAS at baseline combined with DWI <1000 may predict a relatively quiet disease course.

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Recent liothyronine price increases have changed primary care prescription practice, with increased referrals to specialist care

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Background
The cost of liothyronine (T3) has significantly increased, possibly affecting prescription practices.
Methods
An online questionnaire was designed to assess current T3 use by UK endocrinologists and to determine whether the price increase resulted in a change in primary care prescription practices. Consultant grade members of the Society for Endocrinology Thyroid Network were invited to partake.
Results
Results were analysed from 50 consultant respondents; the majority (85%) were aware of the recent price increase in T3 and had received queries from GPs reluctant to prescribe T3 in the past month (82%); 73% had received patient queries. While most trusts (63%) had no restrictions in place for T3 prescription, almost half (44%) of CCGs provided guidance regarding restriction of T3 use to GPs.
The majority (82%) found the BTA guidance on T3 use helpful, with most (61%) welcoming further advice.
T3 was prescribed by the majority (73%) of respondents, but very infrequently (84%; <1 patient/month) and mostly due to patient request. Respondents indicated that very few ($<5\%$) patients attending clinic were treated with T3 alone (98%). Only 9% used thyroid extract. Most respondents (57%) are equally likely to use T3 compared with 2 years ago.
Conclusions
T3 is used by the majority of UK consultant endocrinologists to treat hypothyroidism, but very infrequently. Price changes in T3 have raised GP reluctance to prescribe T3, resulting in increased secondary care involvement. Current guidance from the BTA regarding T3 use is well regarded, but further advice given the price changes would be welcomed.

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Association of a promoter BAFF polymorphism in Graves' disease

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Introduction
B lymphocyte activating factor (BAFF), a member of the tumour necrosis factor family, is essential for B cell activation, differentiation and survival. It promotes autoantibody production and as Graves' disease is caused by thyroid stimulating autoantibodies, it is an excellent functional candidate gene. Indeed, elevated serum BAFF levels have been found in patients with several autoimmune diseases, including Graves' disease (GD). The T allele of the BAFF promoter SNP (*rs9514828; -871C/T*) has been associated with susceptibility to the autoimmune conditions systemic lupus erythematous (SLE) in Egyptians, and immune thrombocytopenic purpura in Chinese and German cohorts.
Aim
To investigate whether variants in the BAFF gene are associated with GD in a cohort of UK patients.
Methodology
A case-control association study was performed. *rs9514828* was genotyped in 486 UK GD patients using Taqman chemistry (Life Technologies) and results compared to genotype data from 5158 healthy individuals available from the Wellcome Trust (WTCCC2). Statistical association analysis was performed using PLINK.
Results
There was no significant difference between the frequency of the T allele in UK GD subjects (491/972; 51%) compared to controls (5046/10316; 49%: P 0.34, OR 1.07 [95% CI 0.93–1.21]). Similarly, there was no difference in genotype frequencies between the UK GD cases and controls. The TT genotype was present in 113/486 (23%) cases compared to 1220/5158 (24%) controls, while 265/486 (55%) of cases were heterozygous compared to 2606/5158 (50%) controls (*P* 0.16).
Interpretation and Conclusion
The *rs9514828* SNP is not associated with GD in a UK cohort. This could be related to allelic heterogeneity, with different BAFF SNPs contributing to autoimmune susceptibility in Caucasians, compared to other populations. It is also possible that the genetic variants contributing to multisystem autoimmune diseases, such as SLE, may be distinct from those in single organ-specific autoimmune conditions such as GD.

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P397

Primary versus tertiary care follow-up of low risk well differentiated thyroid cancer

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The optimum approach to long-term follow-up of well differentiated thyroid cancer (DTC) remains unclear. We assessed the outcome of DTC patients followed in primary care (PrC) from Edmonton, AB with tertiary care (TrC) settings from Halifax, NS and London, ON. Patients who met the following criteria were identified: a) Initial diagnosis between January 1, 2006 to December 31, 2011, b) primary tumour
A total of 317 patients, (PrC = 93 and TrC = 224) were identified. Female preponderance (PrC = 83% and TrC = 87%), mean age at presentation (PrC = 46.02 yrs. and TrC = 47.7 yrs., prevalence of papillary thyroid cancer (PrC = 94% and TrC = 96%), mean follow-up (PrC = 62.24 months and TrC = 64.6 months) and mean tumour size at presentation (PrC = 1.35 CM and TrC = 1.26 CM) were similar (all P = NS). All patients had undergone near-total thyroidectomy. The risk of recurrence was similar (PrC = 1.1% and TrC = 1.3%; $P = 0.69$). Recurrences were identified through ultrasound (US) and rising TG in TrC group and only through rising TG in PrC group. There were 3 deaths in TrC (all unrelated to DTC), and no death in the PrC group. Rate of US surveillance was similar (PrC = 60% and TrC = 53%) ($P = 0.21$). There were a mean of 5.25 visits to specialist clinic in TrC group. Serum TSH was outside the target range in 14% PrC and 60% TrC patients.
Our data shows that follow-up of DTC in primary care is a feasible alternative and the outcome of patients in primary care is similar to a specialist centre. Our data support the notion of discharging low-risk DTC to primary care; however, clear guidelines must be provided to the primary care physicians at the time of discharge.

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Predictors of thyroid autoimmunity in Maltese individuals

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Introduction
Autoimmune thyroid disease is a multifactorial disorder, which has been linked to the exposure of certain environmental factors.
Aims and Objectives
To investigate whether thyroid autoimmunity (TAI) is significantly associated with identifiable and potentially modifiable environmental factors in Maltese individuals.

Materials and Methods
A case-control observational study was conducted among 324 Maltese patients, who had been screened for TAI within the previous 12 months. 164 cases (positive thyroid peroxidase [TPO-Ab] and/or thyroid stimulating hormone receptor antibodies [TSH-R Ab]) and 160 controls (negative antibodies) were recruited. A questionnaire sought information on drug history, social/reproductive history, stress and iodine intake, while blood specimens were collected to measure glycosylated haemoglobin, thyroid function, TPO-/TSH-R Ab status, 25-hydroxy vitamin D level and hepatitis C antibody status. A stool sample was collected for *Helicobacter pylori*.
Results
Both TPO-Ab and TSH-R Ab positive individuals were exposed to a higher amount of smoking pack years ($P=0.038$ and 0.037 respectively). No significant predictors of TSH-R Ab positivity were identified on multivariate regression analysis. The odds for TPO-Ab positivity was increased by female gender (OR 2.815 [95% CI, 1.387, 5.714]; $P=0.004$) and discontinuation of smoking (OR 2.367 [95% CI, 1.213, 4.621]; $P=0.012$), while birth in winter (OR 0.470 [95% CI, 0.253, 0.871]; $P=0.017$) and higher intake of iodine rich foods (OR 0.864 [95% CI, 0.761, 0.981]; $P=0.024$) decreased the odds for TPO-Ab development.
Conclusion
TPO-Ab positivity appears to be affected by environmental factors in Maltese individuals, though not all are potentially modifiable.

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Autoantibodies to the thyrotropin receptor in Alemtuzumab-induced thyroid autoimmunity: determination of their biological activity, and possible role as predictive marker of disease

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Background
Alemtuzumab (ALTZ) is a humanised monoclonal anti-CD52 antibody used as effective treatment for relapsing/remitting multiple sclerosis (MS), causing panlymphopenia with subsequent lymphocyte repopulation. Unfortunately, around 40% of patients develop secondary humoral autoimmunity, mainly affecting the thyroid gland. Anti-thyrotropin-receptor (TSHR) autoantibodies (TRAb) can stimulate (TSAb), block (TBAb) or not affect ('neutral') TSHR function, with TSAb causing hyperthyroid Graves' disease (GD), and TBAb hypothyroidism. Low-affinity neutral TRAb could pre-exist in MS patients, then undergo somatic hypermutation to become high-affinity TSAb/TBAb post-ALTZ, causing thyroid dysfunction.
Methods
Sera from MS patients, 11 developing post-ALTZ thyroid autoimmunity (TA; 10 GD, 1 hypothyroidism) and 14 not developing it (NO-TA), were obtained from the Welsh Neuroscience Research Tissue Bank (Cardiff, UK), and evaluated at different time-points: (1) pre-ALTZ, (2) post-ALTZ before the disease onset (TA) or latest time post-ALTZ (NO-TA), (3) post-ALTZ during/after thyroid dysfunction onset (TA only). Flow cytometry (FC) detected any TSHR-binding TRAb. Luciferase bioassays (LB) detected both TRAb presence and bioactivity (neutral/TSAb/TBAb), also deduced from the corresponding thyroid function. TRAb positivity (TRAb+) was defined as FC and/or LB assays positivity.
Results
Among overall TRAb+ cases (all time-points considered), TBAb were 2/7 (28.6%) in GD, 1/1 (100%) in hypothyroidism, and 3/4 (75%) in NO-TA.

Time- points	TRAb+		Fisher Exact *T*-test
	TA	NO-TA	
1	3/11 (27.3%)	0/14 (0%)	$P=0.07$
1+2	5/11 (45.5%)	4/14 (28.6%)	$P=0.43$
3	8/11 (72.7%)	NA	NA

NA = Not Applicable.

Conclusions
(A) Patients with positive TRAb prior to ALTZ had an increased tendency to develop post-treatment TA. Thus baseline TRAb could provide a predictive marker of future development of thyroid dysfunction. (B) TRAb+ patients were euthyroid at time-points 1–2, suggesting the presence of low-affinity antibodies unable to affect thyroid function. (C) Post-ALTZ TBAb subtype is common, and could be responsible for post-ALTZ hypothyroidism, and cases of post-ALTZ Graves' disease with fluctuating thyroid function.

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P400

Activating germline TSHR mutations are rare in adult hyperthyroid patients without autoimmunity and showing diffuse uptake on radionuclide thyroid scintigraphy

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Background
Sporadic and familial autosomal dominant non-autoimmune hyperthyroidism (S/FANH) is caused by activating germline mutations in the *TSH Receptor* (*TSHR*) gene. These patients lack TSHR-Ab, show diffuse uptake on radionuclide thyroid scan and often lack positive family history due to variable penetrance. Because of these overlapping features, S/FANH is difficult to distinguished from Graves' disease without autoimmune features. Therefore, 2012 European Thyroid Association recommends genetic testing for TSHR gene in such patients. However, there is lack of knowledge on the prevalence of these mutations in white-European adult hyperthyroid patients.
Aim
We aim to assess the prevalence of activating *TSHR* mutation in adult hyperthyroid patients with features suggestive of S/FANH (absence of autoimmunity and diffuse thyroid uptake on radionuclide scan).
Method
We retrospectively and prospectively collected clinical data and DNA (from blood/saliva) for adult white-European hyperthyroid patients, who lacked evidence of clinical and biochemical thyroid autoimmunity (absence of Graves' ophthalmopathy or TSHR-Ab) and had diffuse uptake on thyroid scintigraphy. All of these patients underwent genetic test for *TSHR* gene.
Results
We recruited 79 patients from three centres in the south-west, UK. Genotyping was unsuccessful in 4 samples. The genotyping of *TSHR* gene did not identify previously known/novel activating mutation in any patients. One patient had rare likely benign variant (c.1001T>C, P.Ile334Thr, exon 10, population freq = 0.003%). The variant is in the less conserved extracellular domain and it is outside the mutation hotspot region.
Conclusion
Activating germline *TSHR* mutations are rare in adult hyperthyroid patients with diffuse uptake on thyroid scintigraphy but without TSHR-Ab. Our study does not support routine genetic testing for *TSHR* gene in such patients.

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P401

Does presence of 'Coexisting Thyroiditis' affect Radioiodine Uptake in Thyroid Cancer Ablation Doses?

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Background
Patients being treated for differentiated thyroid cancer (DTC) receive a dose of Radioiodine for remnant ablation. Occasional patients appear to have little or no iodine uptake at all in the thyroid bed or else where even shortly after thyroidectomy.
Objective
To evaluate the influence of 'Coexisting Thyroiditis' on radioiodine uptake in thyroid cancer ablation doses.
Methods and Design
Retrospective study of 240 DTC patients who received I-131 remnant ablation, out of which 165 patients met the inclusion criteria. We compared Radioiodine uptake on the nuclear medicine tail-end scan with initial histopathology reports and thyroid autoantibody status. High risk determinants such as lymph node metastasis and extrathyroidal extension were evaluated.
Results
Out of 165 DTC patients 52 (30.7%) had coexisting thyroiditis. Out of 52 patients with thyroiditis, 28 (53.8%) showed poor uptake on the tail end scan compared to those without thyroiditis. $P=0.000$. Patients with thyroiditis also demonstrated low level of extrathyroid extension (17.6%) and lymph node metastasis (34.6%) compared to DTC without thyroiditis. P values 0.003 and 0.064 respectively.
A total of 135 were analysed based on low (1100 MBq) and high (3000 MBq) doses. 98 received 1100 MBq. 13 (37.1%) out of 35 with thyroiditis showed poor uptake while 22 (62.8%) had intense uptake compared to 63 without thyroiditis in the same group 0 (10.6%) poor uptake. ($P<0.001$)
Of the 36 patients in 3000 MBq group, 5 (33.3%) out of 15 with thyroiditis showed poor uptake and 10 (66.6%) showed intense uptake compared to 0% poor uptake and 100% intense uptake in those without thyroiditis. ($P=0.008$)
Conclusion
This study demonstrated 'Thyroiditis effectively inhibited radioiodine uptake in low ablation doses. It was also shown that this beneficial effect brought about by background thyroiditis was overcome by administering higher dose RAI.
Keywords: Differentiated Thyroid cancer, Thyroiditis, Recurrence, Radioiodine, Ablation dose.

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Evaluation of normal reference range for thyroid uptake of technetium-99 m in a single centre UK population

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Objectives
The aim of the study was to evaluate the normal reference values for thyroid uptake using Technetium-99 m (Tc-99 m) pertechnetate.
Methods
Sixty-seven euthyroid patients with primary hyperparathydism who underwent parathyroid imaging with Tc-99 m pertechnetate between January 2012 to April 2014 at the Nuclear Medicine department, Newcastle upon Tyne Hospitals was studied. Electronic medical records and biochemical thyroid function tests were reviewed to confirm that all patients were not on medication or supplements that could affect thyroid function and they were both clinically and biochemically euthyroid within 6 months of the scan. Thyroid uptake values were determined by the dual tracer subtraction protocol.
Results
Median and interquartile uptake range of Tc-99 m pertechnetate in euthyroid patients were 0.9% and 0.5–1.4% respectively. The normal reference range in the study population was 0.2–2.0%. Thyroid uptake inversely correlated with age in the female ($r=-0.40$, $P=0.04$), male ($r=-0.50$, $P=0.04$), and whole group ($r=-0.40$, $P=0.002$).
Conclusion
The normal reference range for Tc-99 m pertechnetate uptake was found to be less than that presently adopted in our institution (1.0–3.5%). However, it was comparable to that observed in recent studies from geographically distant populations. Periodic, location-specific evaluation of normal uptake values is advocated to increase diagnostic precision in thyroid disease.
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P403

Use of glucocorticoids in subacute thyroiditis

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Background
Subacute thyroiditis is a self-limited inflammatory thyroid disorder with a triphasic clinical course of thyrotoxicosis, hypothyroidism, and return to euthyroidism. Whilst glucocorticoid (GC) treatment is advocated for managing moderate-to-severe symptoms, the ideal initiating dose and titration regime is unclear. Traditionally, doses of up to 40 mg of prednisolone have been used. More recently, to minimize adverse effects, a 15 mg initiation dose of prednisolone with a 2-weekly reducing regime by 5 mg has been described but with high disease relapse rates.
Aim
To assess safety and efficacy of our protocol of initiating oral prednisolone 30 mg daily (or equivalent dose of oral methylprednisolone) and reducing by 5 mg every 2 weeks until discontinued. Thyroid ultrasound examinations were also performed at baseline, at one and three months.
Methods
We prospectively collected data on all nine consecutive patients presenting with subacute thyroiditis where GC treatment was used as per our protocol from November 2015 to December 2016.
Results
Patients ranged from 33 to 65 years in age and included five women. Neck pain was seen in all patients; symptomatic improvement occurred within 24–48 hrs of glucocorticoid treatment in all. Full resolution of symptoms with no recurrences was achieved in 7 patients (78%). Two patients suffered symptom recurrence when GC dose was reduced and required extended therapy (28.1 and 32.6 weeks). Two patients developed hypothyroidism requiring levothyroxine at six months. There was sonographic evidence of thyroiditis in all at baseline; following a month of therapy, inflammation had completely (50%) or partially (50%) resolved; only one patient had persistence of mild inflammatory appearances at three months. Side-effects were rare with mild abdominal discomfort in one participant and mild post-prandial hyperglycaemia in another participant.
Conclusion
Our protocol for GC treatment for moderate-to-severe subacute thyroiditis was safe and effective, achieving rapid clinical and sonographic resolution in the majority of patients.
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P404

The impact of a profoma introduction on the accuracy and appropriateness of Synacthen testing

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Background
We previously reported that a high number of synacthen tests are carried inaccurately within our trust with a significant delay in sample collection after tetracosactide injection. We also reported a high number of patients having Synacthen tests unnecessarily. In light of this we introduced a Synacthen proforma and re-audited our results.
Method
A retrospective study was carried out on 36 patients undergoing Synacthen tests between October 2015 and August 2016. Patient records were reviewed to see if a prior cortisol had been measured and the accuracy of the sample timings within the SST were evaluated. The results were compared to original audit data.
Results
There was a significant reduction in the number of Synacthen tests being performed following policy change (0.80 tests/week vs. 1.29 tests/week; $P=<0.01$). There was an associated increase in number of patients having

cortisol levels measured prior to commencing an SST (27/36, 75% vs. 168/322, 52%; $P = <0.01$). A reduction in the proportion of tests being undertaken inaccurately was seen following the introduction of the new policy (12/36, 33% vs. 196/336, 58%: $P = <0.01$). There was a significant improvement in the timing of the samples in those that used the proforma. 30 minute median sample time = 30 minutes (IQR 29/32; range 27-52) vs. 35 minutes (IQR 30–45; range 13–197) $P = <0.01$. 60 minute median sample time = 63 minutes (IQR 60–65; range 57–81) vs. 65 minutes (IQR 60–75; range 30–198) $P = 0.05$.

Conclusion

The introduction of a synacthen proforma has resulted in a reduction in inappropriate synacthen tests and an improvement in the accuracy of sample collection making result interpretation more reliable.

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P405

Metoprolol succinate is associated with better quality of life in treatment of grave's disease

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Background

Grave's Disease (GD) is the most common cause of hyperthyroidism and its effect of health status is well known. Beta blockers (BB) are routinely used to control thyrotoxic symptoms in initial phase of treatment of GD.

Objective

To study the effect of BB on quality of life (QOL) in patients with GD using different BB; propranolol, nebivolol and metoprolol succinate.

Method

A cohort prospective study was conducted on 109 patients with GD (63 females and 46 males in the period between August 2016 till April 2017). Patients were divided into three subgroups; group A (41 patients receiving carbimazole and propranolol 20–80 mg/day), group B (33 patients receiving carbimazole and nebivolol 2.5 mg/day) and group C (35 patients receiving carbimazole and metoprolol succinate 25–50 mg/day). All patients were examined, had thyroid profile and 36-item short form survey) SF-36) questionnaire to assess QOL as a baseline and 1 month later after treatment.

Result

There was no significant statistical difference regarding thyroid profile before and after treatment (P value >0.05), however group C had shown better results on SF-36 questionnaire score than the other subgroups (P value <0.05).

Conclusion

Metoprolol succinate is the best BB for control of thyrotoxic symptoms as it is associated with better QOL than other BB.

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P406

Radioiodine treatment for thyrotoxicosis in a district hospital: a re-audit

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Introduction

Radioiodine is used for the treatment of Thyrotoxicosis when medical treatment (anti-thyroid drugs) has failed or cannot be tolerated and surgical treatment is not an option. Our previous audit in 2011 demonstrated substantial adherence to the Royal College of Physicians (RCP) guidelines for Radioiodine treatment, but one patient was lost to follow-up. It was recommended that we improve our re-call system. We aimed to re-audit our service.

Methods

Notes and blood results for patients with thyrotoxicosis who received radioiodine treatment between January 2013 and December 2016 were retrospectively reviewed for information on pre-treatment, treatment and the post-treatment follow-up period.

Results

One hundred and four patient-notes were retrieved (27 males, 77 females). They had an average (range) age of 57 (21–89) years and duration of thyrotoxicosis of 4 (0.25–15) years. The average (range) radioiodine dose was 637 (513–870) MBq. Hypothyroidism occurred in 88% of patients within 6 months of treatment. As a result 7.7% of patients remained euthyroid and 9.6% continued to have thyrotoxicosis after treatment (a third of these went on to have surgery). Table 1 shows the audit results compared to those of the previous audit done in 2011. There was 100% adherence to all of the standards apart from the 6-week telephone follow-up call for thyroid function test (TFT) results, where one patient was missed, but had appropriate follow-up with the General Practitioner.

Table 1 Audit results compared with those of the last audit

Audit Criteria	Standard (Target)	2011 (1st Cyde)	2017 (2nd Cycle)	Compliance with standards
Patient information sheet given	100%	100%	100%	Fully Compliant
Risk assessment questionnaire filed	100%	100%	100%	Fully Compliant
Informed consent form signed and filed	100%	100%	100%	Fully Compliant
ATDs stopped a week before radioiodine	100%	100%	100%	Fully Compliant
Steroids for thyroid eye disease	100%	100%	100%	Fully Compliant
Yellow information card given to patient	100%	100%	100%	Fully Compliant
Pathology request form for 6 week TFT check	100%	100%	100%	Fully Compliant
Letter sent to GP	100%	100%	100%	Fully Compliant
6-week telemedicine follow-up done for patient	100%	97%	99%	Fully Compliant
Final Compliance	**Fully compliant**			

Conclusion

This audit demonstrates that we are 100% compliant with the RCP guidelines for use of radioiodine for treating thyrotoxicosis. Our results are comparable to that of other centres. We need to ensure that the details of all patients who receive radioiodine treatment for thyrotoxicosis are on our re-call register for the 6-week TFT follow-up.

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P407

Clinical outcomes following radioiodine therapy in Graves' thyrotoxicosis

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Introduction

Radioiodine (RAI) is safe and effective but further information to predict outcomes, specifically treatment failure and residual symptoms following treatment of hypothyroidism, may help improve outcomes.

Methods

Retrospective, observational, single-centre study. Electronic medical record review ($n = 664$) and patient questionnaire ($n = 174$).

Results

Complete cohort: Analysis of outcomes limited to 555 patients receiving first dose of 400 MBq. 77.1% hypothyroid, 5.6% euthyroid, 16.8% hyperthyroid and 3 deceased at 1 year. Treatment failure was associated with higher TRAb (OR 1.8, $P = 0.01$ for TRAb above median); the only significant predictor in a model including gender, age, pre-treatment fT4 and TSH. Pre-treatment with thionamides (51.8% of cases) was associated with a 2.9-fold increased risk of treatment failure ($P < 0.001$). Thionamide after RAI (28.0%) carried a 2.3-fold increased risk of failure ($P < 0.001$).

Questionnaire

31% were current smokers at the time of RAI. Thyroid eye disease was present in 10.9% prior to treatment and in 19.0% after. Median weight change was +6.0 kg (IQR 3.6–7.4), with multiple regression identifying only higher pre-treatment fT4 as a predictor of weight gain ($P = 0.03$). 59.6% reported weight gain (A), 51.8% required more sleep since RAI (B), 44.4% felt less energetic (C), 41.8% felt slower mentally (D) and 42.4% reported more difficulties with memory (E). Logistic regression identified female gender (A,B,C); higher levothyroxine dose (A,B); and lower fT4 (A,D,E) as independent predictors of greater symptoms following RAI. 79.4% would recommend RAI to a friend.

Conclusions
- TRAbs may be a useful tool in stratifying radioiodine dose.
- Thionamide therapy may increase treatment failure risk, independently of disease activity.
- Patients are largely satisfied with RAI despite high prevalence of symptoms.
- Greater symptoms in those with lower fT4 despite larger dose of levothyroxine raise questions regarding optimal replacement therapy.

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P408

Thyroid Nodules ($n=400$): Correlation of TI-RADS' score with cytological results

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Introduction
Nowadays, thyroid Ultrasound (US) is a reference exam and the best way for detection, diagnosis and monitoring of thyroid nodules suspect of malignancy. It allows selection of suspicious thyroid nodules for malignancy.
Our aim was to assess contribution of this exam using the TI-RADS score in order to establish the correlation with cytological results.
Materials and methods
A prospective study of 395 patients recruited within 12 months (2015–2016) was conducted leading to 400 samples. The Endocrinologist practiced himself thyroid US coupled with Doppler mapped each nodule according to the TI-RADS followed by a FNA including a sampling of the product by capillarity.
Cytological analysis was done by an experimented cytologist, in a center considered as a reference. Results were classified according to Bethesda's classification.
Results
Among the 400 cytological analyses, 333 were classified as benign (83%), 11 were suspect of malignancy (3%) and 19 malignant (5%). The remaining 37 (9%) were difficult to classify and needed to be controlled.
Histological examination confirmed malignancy in the 30 suspicious and malignant cytological cases.
After comparison with US data it was found a TI-RADS' score sensitivity of 88%, specificity of 92%, negative predictive value (NPV) of 98% and a positive predictive value (PPV) of 52%.
Conclusion
In this study, the PPV may be explained by focal thyroiditis frequency: the main differential diagnosis of thyroid carcinoma. Consequently, the integration of TI-RADS' score data to the results of FNA remains a valuable approach to ensure a better thyroid nodules exploration.

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P409

Orbital decompression surgery for graves' ophthalmopathy

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Introduction
Graves' disease is an autoimmune disorder of the thyroid gland causing over-production of thyroid hormone. Although this disorder can lead to systemic changes throughout the body, the most common extrathyroid manifestation of Graves' disease is ophthalmopathy. Patients can have significant ocular prominence from the increase in intraconal and extraconal fat and muscular hypertrophy. This can lead to vision changes, decreased ocular motility, and corneal injury from lid retraction. In patients that have failed medical management or patients with significant or progressive visual symptoms, surgical decompression can be a useful treatment modality.
Methods
We present a retrospective review of all patients where orbital decompression surgery was performed to treat thyroid-related ophthalmopathy from 2014–2017. All cases were performed by a single surgeon (T.P.). Patient age, demographics, medical history and symptomology, pre and post-operative Hertel measurements were collected. Subjective response to surgical treatment was also recorded.
Results
A total of twelve patients, ten females and two males, underwent surgical decompression surgery for Graves' ophthalmopathy. Six patients underwent the surgery in both eyes, the other six underwent the surgery only for one eye. Four of the patients' main complaint was dry eyes, two patients had diplopia, two patients complained of severe pain and pressure. Preoperative Hertel exophthalmometer readings ranged from 18–24, with improvement ranging from 1–5 mm. All patients underwent decompression by removal of intra/extraconal fat in upper and lower eyelid compartments. Ten orbital floor and medial wall ostectomies were performed. Post-operatively patients reported decreased swelling, resolution of double-vision, and improved aesthetic appearance.
Conclusion
Orbital decompression surgery is a useful treatment option in patients with significant Graves' ophthalmopathy, providing both a functional and aesthetic improvement of symptoms.

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P410

Adoption of the British Thyroid Association guidelines for the investigation of thyroid nodules: a district general hospital experience

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Background
The British Thyroid Association's thyroid cancer guidelines (2014) advocate the U1-5 nodule grading system as a primary diagnostic and classification tool.
Aims
We assessed whether practice reflected guidelines, and examined patient outcomes.
Methods
Patients with a thyroid ultrasound, undertaken by radiographers or general radiologists, in January-June 2015 were identified. Investigation and outcomes over 18 months post-ultrasound were examined.
Results
Thyroid ultrasound was graded in 57 of 60 patients (U2, $n=10$; U3, $n=37$; U4, $n=6$; U5, $n=4$). Of 10 patients with U2 grading, 3 had fine needle aspiration (FNA), all graded Thy2; of the remainder, one underwent thyroidectomy (benign) and 2 had stable imaging. 32 of 37 patients with U3 grading had FNA: those graded Thy2 ($n=15$), Thy1 ($n=3$) and with discordant Thy2/Thy3 on repeated sampling ($n=2$) had subsequent stable imaging or benign lobectomy; 10 patients with Thy3 underwent lobectomy (malignant ($n=5$), benign ($n=4$)) or were downgraded on MDT discussion ($n=1$); 2 patients with Thy 4/5 FNA had malignancy confirmed. Of 6 patients with U4 grading, radiologist review (locally ($n=2$), MDT ($n=2$)) following Thy1/2 biopsy allowed downgrading to U2/U3 in 4 cases, one was a hot nodule and one hemithyroidectomy was benign. Of 4 patients with U5 grading, 2 thyroidectomies identified malignancy, and 2 were benign (on hemithyroidectomy following MDT downgrading to U3 and FNA ($n=1$) or MDT downgrading to U3 and FNA alone ($n=1$)). Ultrasound gradings were altered following MDT review in 6 cases, allowing hemithyroidectomy to be avoided in 5 of these. Overall, the 10 patients with confirmed malignancy had initial ultrasound gradings of U3 ($n=7$), U5 ($n=2$) and ungraded ($n=1$).
Conclusion
Almost all patients received graded ultrasound reports, reflecting early guideline adoption. Results support safe discharge for U2 nodules. U3 grading was common, and this will be compared to specialised centres. Regional MDT discussion avoided 5 hemithyroidectomies.

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P411

Audit of Fine Needle Aspiration Cytology in the Management of Thyroid Nodule: 3-year experience from Scunthorpe General Hospital

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Abstract withdrawn.

P412

A rare case of Moyamoya disease in association with Graves Disease in a Caucasian female

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Moyamoya disease is a progressive chronic neurological disease due to multiple narrowing of the carotid arteries. It can be seen in association with atherosclerosis, vasculitis, haematological conditions, connective tissue disease, neurocutaneous syndromes and certain autoimmune diseases. Very few cases have been reported in association with Graves disease and the majority being in the East Asian population. We present a rare case of this association in a young Caucasian lady.

A 25 years old lady admitted under the stroke team with expressive dysphasia and right sided facial weakness, 3 weeks prior to that she had low grade fever, weight loss and she went down two dress sizes. There were no other dysthyroid symptoms. She smoked, had used illicit drugs in the past and had a history of depression.

On examination, she had expressive dysphasia, drooping of the right corner of the mouth and deviation of the tongue to the right. Her right plantar was upgoing and had no sensory neglect or inattention.

CT head confirmed a Right MCA infarct. She was investigated for causes of stroke −negative vasculitic and autoimmune screen, normal Echocardiogram, glucose and lipid profile. However, she was found to have a raised fT4 of 52.4 and undetectable TSH level. On thyroid examination, she had no signs of thyroid eye disease, had a diffuse palpable goitre with a regular pulse.

She then had an MRI brain which showed an acute infarct in the left putamen with few surrounding lesions of infarct within the left MCA territory. There was marked narrowing of the supraclinoid internal carotid arteries bilaterally characteristic of Moyamoya disease.

She did well on titration of Carbimazole and was seen in endocrine clinic with no residual neurological deficit. It is important to maintain euthyroid status as the return of elevated thyroid levels has been reported with worse neurological outcomes.

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P413

Radioiodine treatment phone clinic for benign thyroid disease: A service audit and quality improvement project in a large tertiary hospital

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Background

Radioiodine treatment (RIT) for benign functioning thyroid disease is an effective treatment for patients with hyperthyroidism. The safety, preparation, administration and follow-up of treatment demands time and organisation. The planning of this elective treatment is affected by the patient's availability which makes adequate and timely treatment of the subsequent hypothyroidism challenging. A quality improvement project was therefore set up to mitigate this.

Methods and Results

We audited the RIT phone clinic (RITPC) at UCLH from January 2015 to December 2016. We established a RIT referral pathway with set follow-up arrangements which ensured a smooth transition from hyperthyroidism to treated hypothyroidism. A total of 47 patients were treated under the RITPC over the 24 months. Suitable patients were identified during the face to face appointment, before referral. During RITPC, our endocrine team made a detailed assessment, with completion of a safety questionnaire, consent and request of RIT. The timing of RIT was entirely dependent upon patient's availability which was helpful in minimising non-attendance rate. The patient was then reviewed at RITPC with monthly thyroid function tests three consecutive months post therapy. Appropriate initiation of thyroxine replacement was judged by the reduction of free $T_4 < 12$ nmol/l and TSH > 5 miU/l. The average dose of 627 Mbq was prescribed by a nuclear medicine physician (JB). Of the 47 patients 33 had Graves' disease (1 required repeat treatment) and 14 had toxic multinodular goiter or toxic adenoma. Overt hypothyroidism was evident in 15 patients by the second month, 11 patients by the third month and 13 patients by 4 -6 months post treatment. There were no reported non-attendances for the patients who were referred for RIT during the three months follow-up.

Discussion

We have established an effective and efficient outpatient pathway which is safe and convenient for patients with a minimal non-attendance rate.

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P414

Pitfalls in the diagnosis of TSHoma vs Resistant Thyroid Hormone Syndrome.

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65 yr female presented with headaches, heat intolerance and loose stools. She had cerebrovascular accident, osteoporosis and vitiligo. A 24 hr ECG revealed atrial flutter with heart rate upto 117 beats /minute. Her medications include warfarin and bisoprolol.

A Thyroid function test (TFT) revealed Free T4 (Ft4): 32 pmol/L (9-19) Free T3: 7.97 pmol/L (3.6–6.5), TSH: 5.7 mU/L (0.35–4.94). Other anterior pituitary function tests were normal.

In view of toxic symptoms an MR scan of the pituitary was done. It showed a right sided microadenoma suggesting the possibility of a micro-TSHoma.

Blood tests revealed alpha subunit levels were normal but sex hormone binding globulin (SHBG) was raised.

Subsequently the thyroid hormone receptor beta genetic screening test was positive confirming the presence of Syndrome of Resistance to thyroid hormone (RTH).

To rule out a co-incident micro-TSHoma a methionine PET scan was done (protocol by Dr Gurnell, Cambridge) confirming a metabolically active lesion. A TRH test revealed a brisk TSH response. An Octreotide suppression test (OST) followed by a trial of Somatostatin analogue (SSA) was then done to differentiate between a TSHoma and pituitary incidentaloma.

The OST test showed a baseline TSH of 4.7 mU/L (0.35–5.5) and 5 hrs of 2.6 mU/L. A depot SSA trial did not show normalisation of thyroid function test. The one year repeat Pituitary MRI showed unchanged appearances along with lateralised PET scan uptake.

Discussion

Both TSHoma as well as RTH are rare syndromes. Though the genetic test was positive for RTH some of the investigations including SHBG, MRI pituitary and positive PET were suggestive of coexistent micro-TSHoma. A six month trial with SSA failed to normalise TFT. This suggested a pituitary incidentaloma rather than a micro-TSHoma, avoiding surgery. Our case demonstrates the challenges faced in diagnosing and differentiating a micro-TSHoma from a pituitary incidentaloma when an RTH syndrome is present.

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P415

A rare case of carbimazole-induced acute liver failure

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Antithyroid drugs can cause hepatic dysfunction, from mild derangement to severe, fulminant failure. It is well known that propylthiouracil may cause fulminant liver failure yet we present an exceptionally rare case of this type of adverse drug reaction with carbimazole.

A 75 year old woman presented to hospital with a fall and a two day history of jaundice. Six weeks earlier, she had been diagnosed with both congestive cardiac failure and Graves thyrotoxicosis, and she was commenced on carbimazole. On assessment after her fall, she was found to be jaundiced and her liver function tests showed significant derangement with a predominantly cholestatic picture. She had no known prior hepatic dysfunction. She underwent liver ultrasound and magnetic resonance cholangiopancreatography, neither of which confirmed an underlying diagnosis. A liver screen excluded viral and autoimmune causes. Carbimazole was suspected as a culprit and therefore discontinued and she proceeded to liver biopsy. The histology showed cholestasis with minimal portal inflammation, which was consistent with a drug induced injury known to occur

with carbimazole. In the meantime, arrangements were made to proceed to total thyroidectomy in order to resolve her thyrotoxicosis. Unfortunately, as her liver failure declined further, she developed sepsis. This lead to a profound clinical deterioration with regards to her congestive cardiac failure in particular. Surgical intervention became extremely high risk due to these comorbidities and was essentially no longer possible and the patient died.
Liver dysfunction with thyroid disease is common, but fulminant liver failure secondary to carbimazole is extremely uncommon. In known cases, the hepatic function is usually cholestatic in nature and recovery is slow after discontinuation of carbimazole. Biopsy specimens show preserved hepatic architecture, intracanalicular cholestasis and perioportal inflammation. This case highlights exceedingly rare potential for carbimazole to cause severe and irreversible liver failure, which may ultimately lead to fatality.

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P416

Myopathy and dyshagia cause by Severe Hyperthyroidism

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Severe hyperthyroidism, along with several other endocrinopathies, is well recognised as a cause of myopathy. This myopathic clinical picture varies from mild myasthenia to profound muscular weakness. We present the case of a 61 year old female (Ms SM), with learning difficulties, who presented with a short history of reduced mobility and anorexia. She was noted to have hypernatraemia and acute kidney injury on admission, secondary to poor oral intake and new onset dysphagia. After being transferred to an endocrine ward, upon noting the presence of a goitre, routine thyroid function tests were performed which revealed profound thyrotoxicosis (Free T4 of 83.1 pmol/L and TSH <0.01 mU/L). Ultrasound scanning of the neck revealed gross bilateral thyroid lobe and thymic enlargement, with a non-homogenous echo pattern and several hypoechoic and isoechoic nodules with no increased vascularity, appearances consistent with a hyperplastic multi-nodular goitre.
A detailed speech therapy assessment revealed severe oral stage dysphagia and enteral feeding via a Nasogastric tube was advised. Ms SM promptly commenced a tailored feeding regimen and anti thyroid medication (carbimazole 30 mg once daily).
An EMG performed 3 weeks after admission showed normal sensory and motor conduction in the distal upper and lower limbs, however, as suspected, also showed pronounced myopathic changes in the muscle tested (the right bicep). Ms SMs thyroid function was monitored closely, and required an increase of the carbimazole dosing to 60 mg once daily. She continued to receive supportive management, with input from the nutrition and physiotherapy teams and managed to regain her normal level of physical function 5 weeks into her admission.
This case visibly demonstrates the profound effect severe uncontrolled hyperthyroidism may have on an individual's physical status, and overall health, as well as specifically showing the rarely seen myopathic changes that occur at the level of the muscle.

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P417

Results of the Liothyronine audit looking at the improvements seen in over all physical well being, mental concentration & somatic symptoms in patients before & after starting T3 + T4 combination

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Many patients continue complaining of subjective symptoms of hypothyroidism despite being on adequate doses of levothyroxine. There are about 14 studies involving T3 + T4 combination including 7 which were rigorously conducted. Majority of them (11 studies) did not show any benefit of combination therapy. But our local experience has been a little different. We looked at small cohort of 15 patients who were on combination T3 + T4 for more than 6 months and were asked to give their self assessments with respect to physical well being, mental concentration and somatic symptoms (brittle nails, hair fall, dry skin, constipation) before and after starting T3 + T4 treatment.
2/3rd of all patients had improvements in symptoms after starting combination treatment. 33% (5patients) stated HUGE improvements in their symptoms, 20% (3patients) reported SIGNIFICANT improvements while 13% (2patients) reported SOME improvements. There were 2 patients (13%) who claimed to have NO improvements at all and another 2 (13%) did not attend the clinic. 1 patient (7%) said she could not decide whether there was any improvement or not.
Conclusion
With 33% of patients stating huge & 20% reporting significant improvements, a total of 53% patients in this audit showed good improvement in their symptoms with combination therapy. Therefore T4 + T3 combination was a good option for treating more than half of the euthyroid patients who continued to complain of subjective symptoms of an under active thyroid. Hence we recommend a trial of T3 T4 combination therapy for all patients who have persistent subjective symptoms despite being adequately replaced with thyroxine.

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P418

Thyroid related adverse effects of Alemtuzumab in patients with multiple sclerosis- Experience from a single tertiary level centre

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Abstract withdrawn.

ePoster Presentations

Adrenal and Steroids

EP002

Transient adrenal insufficiency secondary to chronic opioid drug therapy

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Introduction
Opioid drugs are used frequently for the management of moderate-to-severe chronic pain. Whilst their use is known to impact on endocrine function, this impact is not always well described. We present an unusual case of opioid-induced primary hypoadrenalism, which fully resolved on withdrawal of opioid medications.
Case
A 54-year old female presented with a 13-month history of severe thoracic arthritic pain, for which she was taking Tramadol 100 mg four times daily and Oromorph 10 mg as required for that period. She complained of fatigue and dizziness and had buccal hyperpigmentation. Short synacthen test (SST) revealed a basal cortisol of 38 nmol/L and a raised basal ACTH at 103 ng/L. CT of the adrenal glands was unremarkable. Adrenal antibodies were negative. Renin was 1.2 pmol/ml/hr and aldosterone was <78 pmol/L. A long synacthen test showed a peak cortisol level of 796 nmol/L (normal <900 nmol/L). The patient was commenced on hydrocortisone therapy, which led to improvement of her symptoms and reversed her hyperpigmentation. 3 months later, repeat SST confirmed on-going hypocortisolaemia. 9 months later, she started Pregabalin 75 mg twice daily, physiotherapy and acupuncture. Her opioid drugs ceased. 20 months after initial presentation, full recovery of the adrenal axis was confirmed on three separate SSTs, with appropriate peak cortisol of 566 nmol/L at 60 minutes and a drop of basal ACTH to 25 ng/L (latest test).
Discussion
This case suggests that prolonged use of opioids may mimic adrenocortical failure. It is known that opioids inhibit the hypothalamic–pituitary–adrenal (HPA) axis at multiple levels, but primary hypoadrenalism secondary to their use is not as well described. Opioid endocrinopathy has been documented as early as the 18th century and opioid therapy, as a cause of adrenal insufficiency, primary or secondary, is a possibly under-recognised endocrinopathy with potentially life-threatening adverse effects. This seemed to reverse on cessation of therapy.

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EP003

A challenging case of primary aldosteronism presenting in pregnancy

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Primary aldosteronism (PA) uncommonly presents during pregnancy. Uncontrolled blood pressure may result in adverse maternal and fetal outcomes. We report a case presenting in pregnancy whose management proved particularly challenging, due to variable compliance with therapy, frequent non-attendance at clinic, a subsequent pregnancy and negative imaging.
A 24 year old woman presented at 26 weeks gestation with severe pre-eclampsia and hypokalaemia (2.1 mmol/l). She received intravenous potassium and underwent emergency caesarian section. Investigation postnatally revealed a significantly raised aldosterone/renin ratio at >12250 (aldosterone 2450 pmol/L, plasma renin activity <0.2 pmol/mL/h). Oral potassium replacement was commenced. Plasma aldosterone remained elevated (1580 pmol/L) following intravenous saline loading, confirming a diagnosis of PA. Spironolactone was commenced. CT and MRI scans showed normal adrenals.
She remained hypokalaemic and hypertensive despite being prescribed spironolactone and potassium supplements. Compliance was poor. Further investigations were planned but she defaulted from follow-up. Twelve months after initial presentation she became pregnant again. Spironolactone was stopped. She struggled with potassium supplements due to vomiting and remained hypokalaemic. She was subsequently treated with amiloride and labetalol during the pregnancy and delivered a healthy baby boy at nearly 34 weeks gestation following elective caesarean section.
Postpartum, poor treatment compliance continued. Glucocorticoid remediable aldosteronism was excluded. Repeat adrenal imaging was normal. Adrenal vein sampling (AVS) indicated right adrenal aldosterone excess. Right adrenalectomy was performed and a small adenoma identified. She remains normotensive and normokalaemic off treatment postoperatively.
There are less than 50 published case reports describing PA in pregnancy. Spironolactone is not recommended; epleronone or amiloride can be considered, along with potassium supplements. There is an increased risk of maternal and fetal morbidity and mortality, including preterm delivery, placental abruption and end-organ damage. Our patient's first child had multiple medical issues. This case also highlights the importance of AVS which confirmed unilateral aldosterone production despite normal imaging and enabled cure of her PA.

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EP004

An unusual case of acute adrenal insufficiency

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Adrenal insufficiency is an uncommon endocrine condition with an incidence of 4 cases per million. Common non-iatrogenic causes include autoimmunity, infections and infiltrations. We describe a case of acute adrenal insufficiency secondary to an unusual cause.
A 77-year old female was admitted under the surgeons with abdominal pain and pyrexia. Abdominal ultrasonography showed large stones within a thickened gallbladder and a probable diagnosis of acute cholecystitis was made. All microbiological tests were negative and she was commenced on broad-spectrum antibiotics. Her condition deteriorated with hypotension and she was transferred to the intensive care unit. Abdominal CT scan revealed additional findings in the form of a non-occlusive IVC thrombus, hepatic vein thrombosis and bilateral adrenal enlargement reported as 'possibly bilateral adenomas'. Following intensive treatment she improved and was discharged with long-term antic-oagulation and a clinic appointment to investigate adrenal masses.
4 weeks later, she was readmitted with dizziness, hypotension and acute kidney injury. A synacthen test confirmed adrenal insufficiency and she was commenced on hydrocortisone replacement. Repeat CT scan showed complete resolution of previously noted bilateral adrenal enlargement and a diagnosis of adrenal haemorrhage was made. Repeat synacthen 3 months later, demonstrated persistent hypocortisolism. Interestingly, the cause for simultaneous occurrence of bilateral adrenal haemorrhage and IVC occlusion remains unclear and haematological investigations are awaited. She remains well on replacement with hydrocortisone and fludrocortisone.
Our patient highlights several important messages. Hypocortisolism should be considered in patients with severe sepsis with persistent hypotension despite aggressive management. Adrenal insufficiency caused by adrenal haemorrhage may be present in 15% of patients who die of septic shock. In $>90\%$ of patients the condition is irreversible, confirmed in our case with delayed reassessment of adrenal reserve. This case also emphasises that incidental adrenal masses should be promptly investigated when identified in the setting of an unwell patient.

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EP005

A rare occurence of adrenal leiomyosarcoma

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Leiomyosarcoma is a rare, malignant tumour that can arise from smooth muscle cells anywhere in the body; common sites include uterus, GI tract and retroperitoneum. We report an unusual case of a patient with an adrenal incidentaloma confirmed as a leiomyosarcoma on histology.
A 61-year-old Caucasian female was investigated for chronic abdominal pain. CT scan of the abdomen and pelvis did not show any pathology other than an incidental 2.3 cm right adrenal nodule. She underwent CT and MRI of the adrenals to further characterise the lesion. These were reported as 'indeterminate' but likely a benign adrenal incidentaloma. Patient was then referred to our Endocrinology department. Hormone testing confirmed a non-secretory nodule. A follow up CT adrenal scan at 6 months showed an increase in the size of the tumour to 3 cm, of heterogeneous density with delayed washout of contrast with a low-enhancing centre, requiring an urgent referral for surgery. Although the pre-operative investigations suggested an adrenal tumour, at surgery the tumour was even larger and found to be invading the IVC and was clearly malignant. A planned laparoscopic procedure was changed to an open procedure and a grade 2

right peri-adrenal leiomyosarcoma was resected with resection of the lateral wall of the IVC. Interestingly, the attached adrenal gland was normal.
This case highlights the importance of appropriate radiological assessment in adrenal incidentalomas by experienced adrenal radiologists. Monitoring of patients with suspicious looking lesions even if not meeting the initial criteria for surgery should be rigorous and discussed in a dedicated multi-disciplinary team.
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EP006

Rare case of bilateral massive adrenal myelolipoma in association with congenital adrenal hyperplasia

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Introduction
Adrenal myelolipomas are rare small benign tumours composed of mature fat and hemopoietic tissues, which can be associated with congenital adrenal hyperplasia (CAH). We report a rare case of massive bilateral adrenal myelolipomas.
Case report
A 48 year old gentleman with CAH diagnosed during childhood presented at a routine endocrine appointment. He had not regularly attended his appointments or taken his steroids for over seven years. Clinical examination at that time revealed bilateral enlarged testicles with a perineal scar from previous genital surgery along with a palpable abdominal mass. Coincidentally the patient had recently undergone an abdominal ultrasound organised by his primary care physician for suspected cholecystitis. The scan revealed bilateral abdominal masses which were subsequently characterised by CT abdomen as bilateral massive adrenal myelolipomas displacing abdominal viscera (right adrenal measuring 20 cm & left adrenal, 18 cm). Initiation of steroid therapy resulted in testicular shrinkage, erectile dysfunction and decline in early morning testosterone from 11 nmol/l to 0.3 nmol/l [normal = 8.3–27.8 nmol/l]. In preparation for adrenalectomy detailed adrenal vasculature imaging was performed. He subsequently underwent successful elective bilateral adenalectomy of a 2.9 kg right adrenal measuring macroscopically 27 × 21 cm, 2.1 kg left adrenal measuring 25 × 15 cms and 85 g left adrenunculus. Histology showed completely excised myelolipomata with unremarkable medullary tissue with no evidence of malignancy. He made a good post-operative recovery and was discharged home on prednisolone, fludrocortisone and testosterone replacement.
Discussion
Various theories have been proposed, but etiopathogenesis of adrenal myelolipomas still remains unclear. Being off steroids in the presence of CAH was probably the causative factor in our patient. Small tumours less than 5 cms can be managed conservatively with annual follow up but larger and the symptomatic tumours usually require surgical resection. Several cases of unilateral massive adrenal myelolipomas have been reported but bilateral massive adrenal myelolipomas are extremely rare.
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EP007

Respiratory muscle weakness and diaphragmatic failure secondary to cushing's syndrome

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Respiratory muscle weakness and diaphragmatic failure is a rare presentation of hypercortisolism. We report a case of Cushing's syndrome in a 60-year-old female with history of rheumatoid arthritis, biliary cirrhosis and hypothyroidism. She presented to the Respiratory Physicians with progressive worsening of shortness of breath. Clinical assessment excluded infective pathology, cardiac failure or asthma. Pulmonary function tests (PFT) showed restrictive defect and reduced transfer factor, but high-resolution computer tomography scan did not show pulmonary fibrosis. Sequential chest X-rays/CT and PFT were unable to ascertain the diagnosis despite worsening dyspnoea. Lung biopsy showed non-specific changes and she was considered for lung transplantation. During this period the patient required ITU admission for severe respiratory failure secondary to pneumonia. During this admission, ultrasonography (USG) noted severe reduction in diaphragmatic movement. Respiratory muscle tests confirmed global respiratory muscle and diaphragmatic weakness. Electromyography and nerve conduction study were normal and investigations for myasthenia were negative. During the post-discharge follow-up, she was noted to have features of Cushing's syndrome, disproportionate to the previous use of steroids, and she was referred to our clinic. In addition to the typical facial and truncal appearance she had worsening hypertension and significant weight gain. Urinary cortisol ranged between 250 and 500 nmol/24 hr, post-dexamethasone cortisol was 477 nmol/l and ACTH < 5 ng/L confirming the diagnosis of ACTH-independent Cushing's syndrome. Abdominal CT scan showed 2.6 cm enhancing mass in the left adrenal. Following successful adrenalectomy her symptoms and objective parameters of respiratory function, respiratory muscle strength and diaphragmatic movement demonstrated significant improvement.
Only few cases have been reported respiratory muscle weakness sufficient to cause significant respiratory insufficiency in patients with Cushing's syndrome. However, unlike our patient none of them had diaphragmatic failure. This case highlights the need to consider this unusual manifestation of Cushing's syndrome in an appropriate context.
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EP008

Glucocorticoid and mineralocorticoid Insufficency on treatment with tramadol

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A 30 year old female presented with recurrent episodes of collapse with hypotension. She had been taking tramadol 100 mg four times daily for pain due to endometriosis. A random cortisol of 110 nmol/L led to suspicion of opiate induced adrenal insufficiency and further investigations were undertaken.
Results
09:00 hours ACTH 3.2 ng/L, cortisol 109 nmol/L, fT4 12.3 pmol/L, fT3 3.7 pmol/L, TSH 1.18 mU/L, FSH 6.8 IU/L, LH 12.1 IU/L, prolactin 438 mU/L and IGF-1 14 nmol/L.
Short Synacthen test – cortisol levels 0 min (09:00 h)182, 30 min 397 nmol/L.
Cortisol/ACTH profile (off opiates) following tramadol (half life 6–7 h) 100 mg orally confirmed a fall in both to trough sub-normal levels at eight hours.
Cortisol/ACTH profile (off opiates) following morphine sulphate (half life 1.5–4.5 h) 5 mg orally confirmed a fall in both to trough sub-normal levels at three hours.
On tramadol supine plasma renin activity (PRA) 0.6 nmol/L/h and aldosterone < 100 pmol/L and post-ambulation PRA 1.4 nmol/L/h and aldosterone < 100 pmol/L. Off tramadol supine PRA activity 1.0 nmol/L/h and aldosterone 170 pmol/L and post-ambulation PRA activity 1.6 nmol/L/h and aldosterone 253 pmol/L.
Glucagon test (off tramadol for 3 weeks) confirmed an impaired cortisol response of 304 nmol/L but a normal growth hormone response of 25.3 μg/L.
Whilst adrenal insufficiency due to opiates has been described previously this is the first report of an effect on the renin-angiotensin-aldosterone axis, possibly via suppression of renin secretion. The patient was advised that life-long hydrocortisone (and possibly fludrocortisone) supplements would be required to cover treatment with opiates.
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EP009

Pitfalls in the management of indeterminate adrenal masses

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Introduction
A few adrenal masses may elude characterization on cross-sectional imaging and remain indeterminate. These include lipid-poor adenomas, adrenal metastases and carcinomas and phaeochromocytomas. It is important to distinguish between them, as phaeochromocytomas can be fatal if operated without preoperative blockade. Their clinical spectrum varies, from dramatic symptoms and signs including paroxysmal headache, flushing, diaphoresis, hypertension, tachycardia, to minimal or no symptoms whatsoever. Clinically and biochemically silent phaeochromocytoma is a rare entity.
Case port
We present here a 63 years old woman referred to our department with an incidentaloma of the right adrenal gland on an abdominal computed tomography

scan performed because of chronic back and right subchondral pain. She reported mild, non paroxysmic hypertension well controlled with a combined angiotensin II receptor blocker/thiazide diuretic. She had a cholocystectomy and bilateral hip arthroplasty 5 and 2 years ago. Her physical examination was unremarkable.
The lesion was 4×4.6 cm in size with regular contour, an unenhanced CT attenuation score of 23 HU and delayed contrast medium washout. 1 mg overnight dexamethasone suppression test excluded autonomous cortisol secretion. Aldosterone/renin ratio was normal. Urinary fractioned metanephrines and normetanephrines were in the reference range.
Because of the indeterminate nature of the adrenal mass, she was referred for open adrenalectomy which finally was performed laparoscopically. Intraoperatively the patient developed acute hypertensive crisis successfully controlled with nitroprusside. Pathologic examination of the adrenal mass revealed a pheochromocytoma scored 6 according to the PASS scoring system.
Conclusion
We present the case of a clinically and biochemically silent phaeochromocytoma which provoked an adrenergic spell during surgery. Malignant lesions and phaeochromocytomas may share common characteristics as intense enhancement and slower contrast washout. Suspicious radiologic findings should increase the medical alertness for the possibility of a catecholamine-secreting tumor. Minimal handling of the tumor and perioperative vigilance to combat potential hypertensive crisis are the cornerstones in managing such cases.

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EP010

Idiopathic spontaneous adrenal haemorrhage in pregnancy

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A 24-year-old woman presented at 33 weeks gestation with severe left-sided abdominal pain and orthopnoea. Ventilation-perfusion scan demonstrated two segmental mismatched defects consistent with bilateral pulmonary embolism. Anticoagulation with enoxaparin was commenced. MRI abdomen, carried out in view of abdominal pain, revealed a 4.5 cm left adrenal mass containing a fluid level. Appearances were in keeping with acute left adrenal haemorrhage. Importantly, both scans had been performed on the same day, so she had not been on prolonged anticoagulation prior to detection of the adrenal haemorrhage. There was no evidence of cortisol or androgen excess. She was normotensive.
Short Synacthen test (SST) was blunted with a baseline cortisol of 33 nmol/L, 30-minute cortisol 147 nmol/L and ACTH 8 mU/L (ref <20). SST was performed following administration of high dose betamethasone because of potential early delivery. True adrenal insufficiency was consequently unlikely. 24-hour urine collection revealed normal 5-HIAA and catecholamines. 24-hour urine steroid profile showed raised pregnanediol of 9044 ug/24 h (<1200) consistent with pregnancy. Serum sodium was 136 mmol/L (133–146) and potassium 3.8 mmol/L (3.5–5.0). Thrombophilia screen was negative.
A diagnosis of left adrenal haemorrhage was made. Anticoagulation was continued in view of bilateral pulmonary emboli. The remainder of her pregnancy was uneventful. She delivered at 40 weeks gestation. Post-partum MRI showed a significant reduction in the size of the left adrenal mass, which now measured 1.1×1.8 cm. There were high T1 and T2 signals reflecting blood breakdown products. She was therefore likely to have undergone primary adrenal haemorrhage rather than haemorrhage into an underlying adenoma. Repeat adrenal functional testing was normal.
We illustrate a rare case of spontaneous adrenal haemorrhage in pregnancy. Adrenal cortex hyperplasia and hypertrophy, associated with pregnancy, is thought to predispose the gland to venous congestion resulting in haemorrhage. It should be considered as a potential diagnosis in a pregnant woman presenting with abdominal pain.

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EP011

Isolated DHEAS elevation causing Hirsutism and Oligomenorrhea – A case report

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Hirsutism is an endocrine condition affecting females with growth of unwanted, male-pattern hair secondary to excess androgen activity. The most common cause of hirsutism in females is PCOS (Polycystic ovarian syndrome). Other causes are fairly rare including adrenal and ovarian androgen producing tumours. In 3% of cases no cause of hirsutism is found and these are termed idiopathic[1]. We describe a unique case of a 22-year-old presenting with elevated DHEAS levels with no source identified on imaging. She achieved menarche at age of 13 followed by irregular scanty menstrual cycles and development of excess hair on her back, chin, chest, abdomen, shoulders and inner thighs. Her mother and sister also have hirsutism. Initially she was treated with OCP which did not help with the symptoms. She never complained of acne. She has never been sexually active.
On examination, she had marked hirsutism of the areas mentioned above. Her breast development was at Tanner stage 4. BMI of 27 and BP was 133/77.
Her biochemistry showed elevated DHEAS of 16.6 umol/L with serum Androstenedione of 5.8 nmols/L and normal serum testosterone of 1.5 nmol/L, rest of the endocrine work up including electrolytes, ODST for Cushing's, 17-OH progesterone for CAH, serum prolactin, LH, FSH, progesterone, TFTs, 24 hours urinary steroid profile were all unremarkable. Serum ACTH was 16 ng/L. A transabdominal US did not demonstrate features typical of polycystic ovaries and an endometrial thickness of 4 mm. A dedicated MRI of adrenals glands did not demonstrate any pathology.
The above case illustrates a challenging case of elevated DHEAS causing hirsutism and oligomenorrhea but no adrenal or ovarian pathology identified on imaging. Radetti et al describe a similar case of isolated DHEAS elevation in a 17-year-old male[2]. We recommend that idiopathic elevation in DHEAS should be considered as a rare differential for hirsutism and oligomenorrhea in women.

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EP012

A rare cause of hypertension in pregnancy

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A 23-year-old female with severe resistant hypertension was referred to our Hospital. Her BP on arrival was 240/140 mmHg and she was 13 weeks pregnant. Labetalol had been prescribed previously (200 mg,TDS), with little success in controlling her symptoms. The patient reported headaches, migraines and flushing for several years, especially after eating, and worse during pregnancy. The patient had pre-eclampsia in her first pregnancy.
Prior to transfer, urinary normetanephrine was shown to be elevated (53.4 μmol/24 h, reference range <4.4). MRI of the abdomen revealed a 4.2×3.1×3.5 cm lesion on the left adrenal gland suggestive of a pheochromocytoma. The patient was not on any medications known to increase metanephrines.
On arrival at our Hospital, labetalol was stopped and phenoxybenzamine was prescribed (10 mg,TDS). Propranolol (10 mg) was administered when her HR exceeded 100 bpm lying down.
Plasma metanephrine analysis confirmed an increased normetanephrine (15070 pmol/L, reference range <1180) and an increased 3-methoxytyramine (343 pmol/L, reference range <75). Other than mildly raised white cells 15.6×10^9/L (reference range 3.5–11.0), all other investigations were unremarkable. An USS of the neck showed no abnormalities.
Leading up to the surgery, phenoxybenzamine was increased from 10 mg TDS to 40 mg QDS; propranolol was increased to 30 mg QDS. After adequate α- and β-blockade, a left laparoscopic adrenalectomy was performed (patient was 15 weeks pregnant).
There were no intra-operative or post-operative complications; an abdominal USS performed post-surgery showed no complications to the foetus. The patient's BP stabilised to 118/65 mmHg and she was discharged four days later.
At discharge plasma metanephrines had normalised. Two weeks post-discharge, blood samples were sent for evaluation of *MEN*, *VHL*, *SDHB* and *SDHD* genes. Histological analysis revealed an encapsulated tumor showing infiltration of the capsule and possible minimal infiltration of peri-adrenal fat (PASS score 3). Immunohistochemistry revealed that cells expressed strong diffuse positivity for chromogranin and synaptophysin; thus confirming a PCC.

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EP013

Puzzling adrenal masses in a patient with hypertension

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A 42 year old male was referred to the endocrine clinic with accelerated hypertension (190/110) and an elevated aldosterone renin ratio (59). CT adrenal scan revealed a 16 mm diameter mass in the posterior limb of the right adrenal gland which was confirmed to be hyperfunctioning through adrenal vein sampling. Laparoscopic adrenalectomy was performed and histology confirmed cortical adenoma of the right adrenal gland consistent with Conn's syndrome.

His BP initially normalised post operatively and biochemically his Conn's syndrome had been cured. However over the next 4 months the BP subsequently increased to the point of requiring four antihypertensive agents. MRA of renal arteries showed no evidence of renal artery stenosis but surprisingly showed a right adrenal mass measuring 26 mm in size (despite successful surgery & consistent histology) He also reported deep seated RUQ pain. After discussion at the surgical MDT, a repeat exploration revealed an organised haematoma behind the vena cava. Surgical evacuation was carried out but limited due to its position welded to the vena cava.

His RUQ pain and difficulty controlling his BP persisted so he had a repeat CT A/P five months later which revealed a 35 mm soft tissue lesion in the right suprarenal region thought to represent haematoma or recurrent tumour. Over the next 2 years further imaging with another CT and MRI scan showed no significant change in the right suprarenal mass. Biochemically there was no sign of a functional adrenal adenoma.

Further exploration revealed a cricket ball size inflammatory mass around what was essentially his original surgicel (absorbable haemostatic material from his surgery). Histology confirmed a fibrotic/foreign body reaction. Post operatively his pain has now almost resolved.

This case illustrates 3 different causes of an adrenal mass in the same patient.

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EP014

Delayed diagnosis of neurofibromatosis type 1 associated phaeochromocytoma and intussuscepting sigmoid adenocarcinoma

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Background

Neurofibromatosis type 1 (NF1) related Phaeochromocytoma is a rare endocrine disorder and diagnosis is frequently delayed. NF1 is frequently associated with gastro-intestinal stromal tumour but also reported with adenocarcinoma (rare genetic MLH1 mutation). We presented a case where diagnosis of phaeochromocytoma was delayed 5 years after initial symptoms and only incidentally found on scanning at the time of his presentation with colonic tumour.

History

A 67 year old part-retired farmer presented with altered bowel habits and bleeding per rectum. Subsequent colonoscopy and CT scan revealed an obstructing intussuscepting sigmoid colonic adenocarcinoma (histology confirmed). A heterogeneously enhancing 5 cm right adrenal mass was incidentally found on imaging. On detailed history revealed a 5 years history of hypertension and episodic classical symptoms – light headedness, blurred vision, feeling of impending collapse with pounding chest on straining or sheering sheep. This was previously investigated and diagnosed with vasovagal episodes. Clinically, he had multiple skin nodules presumed neurofibromatoma and axillary freckling. There was no café au lait spots.

Investigation

He had very high (>28 ULN) plasma normetanephrines 2,225 pmol/l and metanephrine 14,448 pmol/l. He was immediately started on alpha blockade and rapid dose titration, he is currently on low fibre diet with a preparation for surgery in a few weeks having a close collaboration with colorectal surgical, adrenal surgical and anaesthetic teams with a potential view of both procedures in one setting.

Discussions

Our patient's diagnosis of phaeochromocytoma was missed despite having typical episodic symptoms, hypertension and neurofibromatoma. This case illustrates challenges of timing safety of anaesthesia (alpha-blockage) and potential untoward complication of delay of surgery for his colonic obstruction. It illustrated an importance role of very careful management in close collaboration with different teams. He is currently awaiting further genetic testing for probable neurofibromatosis type 1 (NF1) and a potential link of gastrointestinal cancer.

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EP015

A case series of metastatic adrenocortical carcinoma at a tertiary care hospital in UK

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Introduction

Adrenocortical carcinoma is a rare malignancy with an incidence of 1–2 per milion population. We present our experience of three patients with adrenal incidentalomas which were subsequently confirmed to be metastatic adrenocortical carcinoma.

Discussion

Our first case presented at 56 years of age with abdominal pain in the background of recent type 2 diabetes and history of alcohol related pancreatitis. CT showed a right adrenal mass more than 100 mm in diameter, multiple lung nodules and a lesion in the liver. He was cushingoid on examination and failed to suppress following overnight dexamethasone with a cortisol of 615 nmol/L. Treatment with metyrapone commenced initially and mitotane introduced one month later. The second case presented at 65 years of age with several month history of polyuruia, polydipsia and worsening fatigue. Initial investigations showed blood glucose of 26.7 mmol/L, potassium 2.7 mmol/L and raised liver function tests. Chest –x-ray revealed two opacities in the right lower zone. Subsequent CT showed $111\times100\times102$ mm heterogeneous mass in right adrenal with metastasis to liver, spine and lung. Patient profoundly Cushingoid with severe proximal myopathy and a cortisol of 801 nmol/L following overnight dexamethasone. Metyrapone started with symptomatic improvement and then switched to mitotane monotherapy. Treatment complicated by multifocal pneumonia and patinet died at approximately two months from diagnosis following respiratory arrest. The third case, presented at 45 years of age with right sided back and abdominal pain. CT showed an 86×81 mm mass in right adrenal with multiple small lesions in spleen. No clinical features of hypercortisolism on examination and following two normal 24-hour urine free metanephrine collection, he underwent successful adrenalectomy.

Conclusion

The majority of patients with adrenocortical cancer present with rapidly progressive Cushings syndrome. In those with limited disease, complete tumor removal offers the best chance of cure while mitotane can be used in those with advanced disease.

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EP016

'Connshing syndrome' as a cause of hypertension: case report

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Introduction

An association between primary hyperaldosteronism and autonomous cortisol secretion, tentatively termed 'Connshing' syndrome, is becoming increasingly recognized.

Aim

To present a case of primary hyperaldosteronism associated with ACTH-independent subclinical Cushing's.

Methods

Clinical examination, biochemical testing and imaging studies.

Results
A 49-year old hypertensive (max 210 mmHg), obese (BMI = 35 kg/m^2), normoglycemic female patient without clinical signs of Cushing's was screened for secondary hypertension, revealing normokalemia (4.1 mEq/L), an increased plasma aldosterone to renin (PAC/PRC) ratio and unsuppressed PAC during the saline loading test (PAC nadir = 10.2 ng/dL, $N < 10$). Cortisolemia was unsuppressed following 1 mg dexamethasone (DEX) overnight (4.66 ug/dL, $N < 1.8$), 2×2 mg DEX (5.74 ug/dL) and 2×8 mg DEX (9.79 ug/dL). 24 hr urinary free cortisol (UFC) levels were normal, but did not suppress with DEX. Contrast-enhanced CT revealed bilateral diffuse adrenal hyperplasia, without identifiable nodules; adrenal sampling was not available. A pituitary micro-incidentaloma, initially found on a head CT scan was not confirmed by pituitary MRI. The patient's hypertension was controlled with the addition of spironolactone. Regular follow-up is being performed to prevent development of clinical Cushing's.
Conclusion
Subclinical Cushing's is possibly underdiagnosed in primary aldosteronism patients, depending on subject selection and tests used for screening of hypercortisolism.

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EP017

Abstract Withdrawn.

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EP018

Iatrogenic cushings syndrome precipitated by fluticasone nasal drops in HIV infected patient

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A 43 year old Somali woman presented with increasing fatigue, difficulty getting out of her chair and 15 kg weight gain over a one month. Past medical history included paranoid psychosis, nasal congestion due to adenotonsillarhypertrophy, and human immunodeficiency virus (HIV). Her HIV infection was well controlled (viral load <50RNA copies/ml), with excellent immunological reconstitution (CD4 count >500 cells/mm^3). Current medications include ritonavir/darunovir, tenofovir, emtricitabine, flupenthixol depot, zopiclone, olanzapine, ferrous sulphate, folic acid and fluticasone nasal spray.
On examination, she had rounded facial facies, truncal adiposity, dorsocervical fat pad and extensive purple striae over the axillae, upper chest, breasts, groin and thighs. Blood pressure was 151/79 and capillary blood glucose 19.4 mmol/L.
Pituitary profile was unremarkable, besides an elevated serum prolactin levels at 1033 mIU/L. Further endocrinology evaluation with low-dose dexamethasone suppression showed plasma cortisol <28 nmol/L (normal range <50 nmol/L) and two low 24 hour urinary free cortisol levels at 28 and 12 nmol/L (normal range <120 nmol/24 h). MRI pituitary was normal.
Her clinical presentation and results were consistent with exogenous glucocorticoid excess. A diagnosis of iatrogenic Cushing's syndrome was made secondary to high systemic steroid levels from inhaled fluticasone, induced by concomitant Ritonavir use.
Her hyperprolactinaemia was attributed to Olanzapine; a common dose-related side effect of antipsychotic treatment. Fluticasone inhalers were slowly weaned and her symptoms, blood pressure and glucose improved.
This case highlights the importance of physicians being aware of the impact of concomitant medication on the adrenal axis, such as co-administration of PI-based antiretrovial regimes and inhaled corticosteroids. Early diagnosis and withdrawal of offending medication will minimise complications from long-term steroid excess.

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EP019

Two cidental lesions: a benign adrenal schwannoma and cerebral meningioma

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We report a case of two incidental lesions, a benign adrenal schwannoma and cerebral meningioma. There are no cases in the literature to link de-novo adrenal schwannoma and meningioma in patients. This case highlights the importance of multidisciplinary working to ensure expedited management in such cases.
A 76 year old gentleman presented to ED with a seizure and a community-acquired pneumonia. Past medical history included atrial fibrillation and ischaemic heart disease, for which he was on warfarin and bisoprolol. CT head revealed a left frontal lobe lesion, radiologically in keeping with a meningioma. As part of his work-up, CT chest/abdo/pelvis showed an incidental left adrenal lesion, approximately 5.5×4.0 cm. On examination, he reported having gained little weight recently, but had no clinical signs to suggest cortisol excess. Abdomen was soft with no palpable masses. Initial biochemistry showed normal electrolytes. His renin/aldosterone, 24-hour urinary catecholamines and overnight dexamethasone suppression tests were normal. Triple phase CT adrenal scan showed an indeterminate solid tumour with no contrast wash-out, and features concerning for a primary adrenocortical carcinoma.
Following discussion at both neurosurgical and adrenal MDTs, despite initial presentation of a seizure, decision was made for left adrenalectomy prior to resection of the meningioma. Clinical priority for this was based on the size of the adrenal lesion and CT appearances being suggestive of adrenocortical carcinoma. Final histology for both lesions confirmed a benign adrenal tumour consistent with schwannoma and a Grade 2 frontal lobe meningioma. There have been no cases of a link between de-novo adrenal schwannoma and meningioma in patients. Adrenal schwannomas overall are very rare tumours that are difficult to diagnose preoperatively, and in the context of possible malignancy, complete laparoscopic excision is the treatment of choice. However, awareness of benign adrenal lesions is vital for accurate pathological diagnosis to guide optimal patient management.

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EP020

The challenge of gender re-assignment in a female pseudohaemaphrodite in a resource poor setting: a case report

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Background
One of the rarely documented endocrine disorders in African setting is pseudo-haemaphroditism. Female pseudo-haemaphroditism (virilized female) is characterized by the presence of 46XX karyotype, ovaries, normal mullerian duct structures, absent wolffian duct structures and virilised genitalia due to androgens in-utero. The commonest cause is Congenital Adrenal Hyperplasia.
Aim
To highlight the challenge in investigating and managing female pseudo-haemaphrodite in a resource-limited setting.
Case presentation
Twenty-one year-old male secondary school drop-out referred from a secondary health facility on account of recurrent bilateral groin pain of 5 months duration with ultrasound scan report of bilateral small testes. Pain was located in the iliac fossae radiating to the groin and cyclical lasting for about 14 days per month. There's history of delayed puberty, small penis and progressive enlargement of both breasts at puberty. He is the 2 nd of a set of twins. The second twin is a female who has given birth to a male child. Examination: a young man with no beard, sparse axillary hair, fully developed breasts, (Tanner stage V), female escutcheon, micropenis: penile length = 4 cm, right testis < 2 mls, left scrotal sac empty. Height = 157 cm, BMI = 19.27 kg/m^2. Pelvic ultrasound revealed intact uterus with tubes and ovaries.
CONCLUSION
Gender re-assignment requires multi-disciplinary approach but the patient is faced with financial, social, cultural and religious barriers. The sex rearing of this index case for the past 21 years is strongly at variance with the true sex of the patient thus resulting in psychological trauma and gender confusion at counseling sessions.
Keywords: Pseudo-haemaphroditism, virilized female, gender re-assignment, delayed puberty.

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EP021

Shortcomings of the short Synacthen test; a near miss case of Addison's disease

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We present a case of a middle-aged lady with clinical features suspicious of Addisons, however an initial false negative short synacthen test (SST), resulted in delay of diagnosis.

Case

A 62-year-old lady presented to ED with a month history of generalised malaise, weakness, dizziness and vomiting. She had a background of type2 diabetes mellitus, previous left parathyroidectomy for primary hyperparathyroidism and B-thalassaemia trait. Admission bloods included Na 129 mmol/l, K 5.6 mmol/l. She had raised infection markers. She received 200 mg intravenous hydrocortisone in ED followed by broad spectrum antibiotics. Chest XR showed small left pleural effusion, not amenable to pleural tap or drainage. Initial SST performed approximately 15 h post hydrocortisone dose, showed good response (Table 1). A few days later, in view of high clinical suspicion, the SST was repeated showing a flat response (Table 1), suggestive of hypoadrenalism. CT chest showed a loculated left-sided pleural effusion, as well as bulky adrenal glands suggestive of adrenal hyperplasia. Adrenal antibodies, remaining pituitary screen, autoimmune and viral screens were negative. TB was excluded. Following her diagnosis of Addison's, she was initiated on hydrocortisone and her clinical symptoms have significantly improved.

Discussion

The initial false negative SST in our patient may be due to the hydrocortisone dose received, although this was 15 h prior. The biological half-life of hydrocortisone is 100 mins, however this may be increased in context of stress, acute illness, certain diseases, and concomitant drugs (e.g. hepatic microsomal inhibitors of cytochrome P-450). Whilst the SST remains the standard screening test for hypoadrenalism, this case demonstrates the importance of ensuring results are interpreted in context of the clinical suspicion. Where clinical suspicion remains high, the test should be repeated, ideally in a non-acute setting to prevent delay of diagnosis.

Table 1

Cortisol (nmol/l)	**Initial SST**	**2nd SST**
Basal	887	229
30 min	805	231
60 min	740	224
ACTH	10.2	**5320**
Renin (nmol/l per hour)	9	
Aldosterone (pmol/l)	<50	

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EP022

When One Diagnosis Reveals Another…

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A 37 year-old gentleman presented following an episode of dizziness while at work operating a fork-lift truck. There was no collapse or associated symptoms. He had been diagnosed with autoimmune hypothyroidism two months previously; commenced levothyroxine, currently at a dose of 75 micrograms daily; and lost ten kilograms in weight. On examination there were no signs of hypoadrenalism aside from a significant postural drop in blood pressure (lying 139/77 mmHg, standing 115/76 mmHg). Biochemistry was typical of hypoadrenalism with serum sodium 130 mmol/l, potassium 5.7 mmol/l and bicarbonate 20 mmol/l. Adjusted calcium was 2.46 mmol/l and renal function stable. Thyroid function tests showed TSH 0.32 mU/l and free T4 14.3 pmol/l. Short synacthen test results revealed cortisol 23 nmol/l at baseline, 24 nmol/l at 30 minutes and 25 nmol/l at 60 minutes. He was commenced on hydrocortisone 20 mg in the morning and 10 mg in the evening with fludrocortisone 50 micrograms daily. ACTH was later reported at 1067 ng/l and adrenal antibodies were positive, confirming Addison's disease. The patient remained lethargic and computed tomography demonstrated a small thymoma. Acetylcholine antibodies were negative and the cardiothoracic surgeons felt no intervention was required. TSH remained mildly elevated with strongly positive thyroid peroxidase antibodies so levothyroxine was re-introduced with good clinical improvement. While studies have shown an increased risk of Addison's disease with Hashimoto's thyroiditis when compared to described background prevalence rates (Boelaert et al, 2010); interestingly a recent review of 3069 Caucasian patients with autoimmune hypothyroidism demonstrated only a near-significant association with Addison's disease when compared with age- and sex- matched controls (Fallahi et al, 2016). 50% of patients with Addison's will present in adrenal crisis (Chakera & Vaidya, 2010), and other case reports describe significant weight loss in this situation (Choudry et al, 2009; Murray et al 2001). This case highlights the need to be aware of this relationship, and to consider hypoadrenalism when symptoms do not improve on levothyroxine replacement, particularly with significant weight loss.

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Bone and Calcium

EP023

MEN -1 with Primary hyperparathyroidism in pregnancy: a report of two cases

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Incidence of MEN1 syndrome is 1/30,000 in general population and incidence of primary hyperparathyroidism (PHPT) in reproductive age women is 8/100,000 population/year. However, coexistent of MEN1, PHPT and pregnancy is extremely rare and true incidence is unknown.

Despite improvements in medical and obstetric care, PHPT in pregnancy remains high risk pregnancy with significant morbidity and mortality.

Case 1: confirmed MEN1 gene mutation with previous distal pancreatectomy for neuroendocrine tumour; was diagnosed to have PHPT during her second pregnancy at age 26 years. Her adjusted calcium was 2.71 (2.2 – 2.6 mmol/L). She remained asymptomatic and was managed conservatively during pregnancy. She delivered healthy boy at 39 weeks gestation. During post-partum period, she underwent parathyroid surgery.

Case 2: younger sister of case 1, with PHPT diagnosed age 14 years and confirmed MEN-1 gene mutation had previously declined parathyroid surgery. At age 28 years, during her first pregnancy adjusted Calcium was 2.88 mmol/L. The management plan including parathyroid surgery was discussed. However she declined surgery due to concerns related to anaesthetic risk mainly increased risk of fetal loss.

At 20 weeks gestation, fetal growth was below 5th centile. Further scan 3 days later confirmed reduced blood flow in umbilical cord with abnormal umbilical artery Doppler PI. Despite close monitoring, adequate hydration, her calcium remained high and she developed pregnancy induced hypertension. The need for Parathyroid surgery was revisited however she declined. Unfortunately, at 24 weeks gestation, fetal scan confirmed intrauterine death.

PHPT in pregnancy is associated with increased maternal (67%) and fetal (80%) complications. Maternal complications include gestational hypertension, pre-eclampsia, nephrolithiasis, bone disease, pancreatitis, hyperemesis, mental status changes, and hypercalcaemic crisis. Fetal complications include intrauterine growth retardation, low birth weight, preterm delivery, intrauterine fetal demise, postpartum neonatal tetany, and permanent hypoparathyroidism.

These 2 cases highlight the fact that PHPT remains high risk and conservative intervention may be appropriate under certain circumstances, however excision of a parathyroid adenoma remains the only definitive treatment.

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EP024

An Unusual Case of Hypercalcaemia Whilst Severely Hypomagnesaemic

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A 68-year-old woman presented with a several month history of nausea, confusion and generalised weakness. In addition, she reported decreased appetite with significant weight loss. She did not report any convulsions, abdominal pain, palpitations, or diarrhoea. Significant past medical history included well-controlled T2DM, hypertension, vitamin D deficiency and GI reflux disease. Importantly, she had no history of renal disease. Relevant medications included

calcium-vitamin D supplements, indapamide and omeprazole. She had no significant family history and did not drink alcohol.
Examination was unremarkable, with no tetany or abnormal reflexes. Neck examination was normal. Blood tests revealed an undetectable magnesium (< 0.25 mmol/L, NR 0.7-1.0 mmol/L), high adjusted calcium of 3.15 mmol/L (NR 2.2-2.6 mmol/L), with a normal phosphate. PTH was inappropriately elevated at 3.9 pmol/L (NR 1.1-6.8 pmol/L), and renal function was normal. Electrocardiogram demonstrated Right-Bundle-Branch-Block.
She was treated with multiple intravenous magnesium infusions and her indapamide, calcium-vitamin D, and omeprazole were stopped. This resulted in normalisation of magnesium and calcium levels with concomitant relief of her symptoms. Neck ultrasound did not identify a parathyroid adenoma. Four weeks post-discharge, her adjusted calcium was at the top of the normal range (2.59 mmol/L) with PTH 5.9 pmol/L, vitamin D 66 nmol/L and magnesium 0.79 mmol/L.
It is likely that this patient has mild hyperparathyroidism which was unmasked by indapamide and calcium supplementation. Omeprazole-use markedly reduced intestinal magnesium absorption. However, the hypercalcaemia caused a functional competition with compensatory renal magnesium reabsorption in the thick ascending limb of the loop of Henle leading to increased magnesium excretion. This was further compounded by the thiazide reducing distal tubule magnesium reabsorption.
This case highlights the need to be extra-vigilant in patients on concomitant PPIs and diuretics as there is a risk of severe hypomagnesemia. Furthermore, this case also provides an example of the unmasking of hyperparathyroidism by thiazides and calcium supplements which further contributed to the hypomagnesaemia.

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EP025

Ribbing Disease: An Unusual Cause of Leg Pain in a Young Woman

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We present the case of a 32 year old woman presenting to her GP with right lower leg pain. This pain was worse at night, but responded to simple analgesia. She was initially diagnosed with arthritis but the leg pain worsened and became bilateral. She had no other significant past medical history with no history of fevers, trauma, fractures or dental problems. She had no relevant family, social or medication history.
On examination, there was no tenderness on bone palpation or active and passive adjacent joint movements. There were no overlying skin changes or joint swellings. Investigations confirmed normal biochemistry including alkaline phosphatase (51iu/L (NR 30-130) and inflammatory markers. Plain radiographs revealed bilateral focal segmental cortical sclerosis involving the mid-diaphyseal region of the tibiae and femora, with resultant narrowing of the medullary cavity. MRI of the lower legs demonstrated associated marrow oedema and bone scanning showed increased tracer uptake in these mid-diaphyseal areas. Bone densitometry however was entirely normal. Based on the clinical and radiological features she was diagnosed with Ribbing Disease.
Ribbing Disease is a rare form of sclerosing dysplasia characterised by benign endosteal and periosteal bone growth confined to the diaphysis of long bones. Most commonly the disease presents with leg pain in young women classically involving the femora and tibiae. It is important to exclude other causes of bone pain including osteomyelitis, fractures, osteosarcoma and Camurati-Engelmann Disease. Treatment is mainly supportive with analgesia but can include bisphosphonates and orthopaedic intervention.
This case demonstrates a rare cause of a common symptom presenting to metabolic bone clinics and highlights the important history, examination and investigation pathway of bone pain.

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EP026

Parathyroid Cysts – An Unusual Cause for Primary Hyperparathyroidism

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We present two patients with an unusual cause of primary hyperparathyroidism. A 50 year old man was referred due to incidentally noted raised serum calcium consistent with primary hyperparathyroidism (adjusted calcium 3.52 mmol/L, phosphate 0.66 mmol/L, PTH (parathyroid hormone) 99.5 pmol/L, Vitamin D 46 nmol/L). An initial neck ultrasound demonstrated a 1.2x1.7 cm left sided presumed parathyroid nodule but also a cystic 3.3x3.2x1.7 cm right sided mass. Isotope MIBI scan was negative. Due to the significantly raised serum calcium, the left sided nodule was excised. However post-operatively, the calcium remained significantly raised requiring inpatient admissions for rehydration. On follow up, fluid from the cyst was aspirated and sent for PTH analysis; PTH was >200 pmol/L. Following surgical removal, the hyperparathyroidism has been cured with histology consistent with a parathyroid adenoma with cystic degeneration.
A 73 year old man had incidentally detected hypercalcaemia by his GP. Investigations revealed adjusted calcium 2.79 mmol/L, PTH 30.0 pmol/L, vitamin D 28 nmol/L, phosphate 0.50 mmol/L. A neck ultrasound showed a 3.5x4.4 cm cystic mass; No solid adenoma was identified. An isotope MIBI scan and 4D CT were negative. His calcium was monitored however it rose to 2.89-3.19 mmol/L despite adequate hydration. Cyst fluid aspirate showed PTH levels >200 pmol/L. He is currently awaiting surgical removal of the parathyroid cyst.
Parathyroid cysts were first described in 1880 and since then, around 300 cases have been described in the literature. They are rare occurrence, with 0.5-1% of all parathyroid lesions being cysts and only 10-15% of these are functional. The majority present with hypercalcaemia or an incidental neck lump. The key to diagnosis is a markedly raised PTH level in fluid aspirated from the cyst. Only 29% of lesions are positively identified on isotope MIBI scan. Non-functional cysts can be treated through aspiration and ethanol ablation. Functional lesions require excision, indication for which is the same as functional parathyroid adenomas. Malignant transformation is rare.

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EP027

Resistance to 1 hydroxyvitamin D? A challenging case

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Hypoparathyroidism following parathyroidectomy is commonly treated with activated vitamin D, (alfacalcidol and calcitriol). Alfacalcidol (1-hydroxyvitamin D) is converted by hepatic 25-hydroxylase to generate calcitriol (1,25-dihydroxyvitamin D) to act on target cells.
We present the case of 66 year old man who was admitted with chest pain in November 2016 and found to have corrected calcium of 1.5 mmol/litre and PO4 2.7 mmol/litre. He had a background of CKD 3, CVA, CCF, IHD, hypoparathyroidism (following parathyroidectomy in 1987) and had been on alfacalcidol 1 mcg once daily since then. He had a prolonged admission from April 2016 to August 2016 following fall and on discharge, his alfacalcidol was stopped (for no apparent reason). Following readmission, he was given intravenous calcium and restarted on oral calcium supplements and alfacalcidol. Despite this, his hypocalcaemia failed to improve regardless of his calcium tablets & alfacalcidol being increased to 1500 mg TDS and 2.5 mcg OD respectively. His liver function tests were normal and CT abdomen did not show any hepatic abnormality. Following this, (in the event of malabsorption) his alfacalcidol was given intravenously but with no improvement, so this was converted to calcitriol 1 mcg OD with correction of his serum calcium within 48 hours.
We advocate that 25 hydroxylation can be impaired without radiological or biochemical markers of liver abnormality. Our case highlights that patients who originally respond to 1 hydroxyvitamin D may develop resistance after a period of treatment, which can be alleviated with use of 1, 25 hydroxyvitamin D instead.

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EP028

A rare case of hypercalcaemia: Double trouble, with a twist

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This gentleman originally presented at the age of 60 years old with slurred speech, confusion and cerebellar signs and was found to have raised calcium and PTH. His sisters, son and daughter were known to have hyperparathyroid-jaw tumour syndrome (HPT-JT) due to a novel germline Leu63Pro missense mutation in CDC73 exon 2. An MRI brain identified cerebellar lesions and he had positive

voltage gated potassium channels; both of indeterminate aetiology following several neurology reviews. There was no evidence of malignancy or lymphadenopathy. He had a right inferior parathyroidectomy and had been normocalcaemic since the operation. His cerebellar symptoms improved.
Two years later he presented with recurrent, acute hypercalcaemia and acute kidney injury following a loading dose of Vitamin D3 (40000 units), with calcium levels of 3.71 mmol/L and suppressed PTH of
He was found to have an elevated serum ACE of 88.8 u/L and with raised IgG (25.5 g/L) and IgA (7.71 g/L). CT showed extensive lymphadenopathy, splenomegaly and lung changes. There was no evidence of parathyroid tumour recurrence. Biopsy of these lymph nodes showed granulomatous inflammation. This suggested sarcoidosis was the cause of hypercalcaemia. 1,25 di-hydroxyvitamin D3 levels were elevated. He was treated with intravenous fluids, bisphosphonates and then prednisolone, when the diagnosis was confirmed. His calcium levels are now stable just above the upper limit of normal.
This is an unusual case of a gentleman with hyperparathyroid-jaw tumour syndrome, associated cerebellar lesions and concurrent sarcoidosis. Although there have been some reports in the literature of hyperparathyroidism and sarcoidosis presenting concurrently, this is the first reported case of sarcoidosis associated with hyperparathyroid-jaw tumour syndrome.

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EP029

A rare clinical presentation of osteomalacia mimicking bony metastatsis in adult

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A 74-year-old man was admitted to hospital with diarrhoea, vomiting, abdominal and lower back pain and reduced urine output. Past medical history included hypertension, angina and hypercholesterolemia. Initial diagnosis was campylobacter gastroenteritis and managed accordingly.
Two weeks later patient developed fatiguability, exertional dyspnoea and joint pain with persistently high creatinine. CT thorax/abdomen/pelvis was performed to look for occult malignancy. This showed diffuse sclerosis of the spinal vertebrae with lytic areas and extensive patchy lysis of the sacrum and iliac bones, which were thought to be secondary to either bony metastases or metabolic bone disease.
Further blood tests showed creatinine of 134 umol/L, PTH 336 ng/L (14-72), adjusted calcium 2.09 mmol/L (2.20-2.60) and microcytic anaemia. Prostate specific antigen, carcinoembryonic antigen and AFP tumour markers were normal. The patient was then referred to endocrinology with low 25-hydroxyvitamin D level of 24 nmol/L (51-250), with calcium of 2.28 mmol/L and PTH 196 ng/L. Creatinine remained elevated at 181 umol/L.
Diagnosed as hyperparathyroidism secondary to vitamin D deficiency and exacerbated by chronic kidney disease. He was treated with cholecalcifoerol 20,000 units weekly for 6-7 weeks followed by 1,800 units weekly. Six months later the patient's 25-hydroxyvitamin D level was 77 nmol/L, his calcium 2.41 mmol/L, his creatinine remained elevated at 189 umol/L, PTH continued to fall at 157 ng/L. Repeat CT scan showed no focal areas of bone sclerosis and no evidence of metabolic bone disease.
Secondary hyperparathyroidism is commonly seen in patients with severe renal failure but can also be a result of vitamin D deficiency or malabsorption syndromes. The underlying pathophysiology is thought to be osteoclast activation and bone resorption resulting in osteomalacia in adults, this leads to joint pain and bone shadowing on imaging that may be mistaken for metastatic disease. This case highlights the need for monitoring of vitamin D levels in elderly patients particularly if they have chronic kidney disease.

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EP030

Hypercalcaemic crisis secondary to a large cystic parathyroid adenoma

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We report the case of an 82-year-old lady who was admitted with hypercalaemic crisis (adjusted Calcium 4.82 mmol/L) and acute kidney injury (creatinine 169 micromol/L). PTH was 295 pmol/L, raising the suspicion of an underlying parathyroid carcinoma. She had no palpable neck mass. Her ALP was 131 IU/L and Vitamin D 73 nmol/L; myeloma screen was negative and chest radiograph showed no pathology. A DEXA scan revealed osteoporosis. The hypercalcaemic crisis was medically managed with intravenous fluids, calcitonin and pamidronate.
Curiously, in 2013 she had also suffered from a hypercalcaemic crisis complicated by acute pancreatitis (Ca 4.69 mmol/L, PTH 180 pmol/L) but had subsequently been lost to follow-up. She had remained clinically well between the two episodes, but had not had any blood tests for calcium levels.
An ultrasound neck identified a 32×21 mm hypoechoic, avascular, cystic lesion which appeared to arise from the right sternoclavicular joint. As the origin was unclear, FNA and MRI neck were performed. FNA was negative for any malignancy. MRI neck demonstrated a well-circumscribed cystic lesion just posterior to the right sternoclavicular joint, which corresponded to a focus of increased activity on the Sestamibi scan.
As the imaging was concordant, a limited approach parathyroidectomy was undertaken. A 3 g nodule was removed and histology revealed parathyroid tissue, composed of sheets of chief cells with a part cystic/papillaroid arrangement, surrounded by a fibrous capsule. Mitoses and atypia were not evident. The appearances were consistent with a cystic parathyroid adenoma. Postoperatively, her calcium was 2.56 mmol/L and PTH 7.9 pmol/L.
This case highlights a rare case of cystic parathyroid adenoma that mimicked parathyroid carcinoma due to very high PTH levels and a suspicious neck mass. Less than 350 cases of cystic parathyroid lesions have been reported in the literature - accounting for just 0.5-1% of parathyroid pathologies.

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EP031

Presenting with hypercalcaemia: 'chicken' or 'egg'?

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Introduction
Hypercalcaemia is a common electrolyte disturbance in patients presenting acutely and can be cause or effect of a multitude of disorders. We present four cases, in which the hypercalcaemia masked or unmasked underlying pathology that may have otherwise gone undiagnosed.
Case series
A 36-year old man presented with acute pancreatitis after completing a marathon. Bloods: adjusted calcium (cCa) 3.16 mmol/L, phosphate 0.50 mmol/L, PTH 24.2 pmol/L. Hypercalcaemia due to primary hyperparathyroidism is a rare cause of acute pancreatitis. It can be unmasked, in the context of significant dehydration.
An 81-year old woman presented with confusion. Bloods: cCa 3.3 mmol/L, PTH 0.5 pmol/L. She had been receiving annual Zolendronate infusions for osteoporosis and cCa had fluctuated at 2.6-2.8 mmol/L. She had missed her most recent infusion. Her diagnosis was PTHrP-driven hypercalcaemia secondary to a pancreatic neuroendocrine tumour. Missing her bisphosphonate allowed for osetoclastic activity and unmasked hypercalcaemia.
A 50-year old woman presented with a 3-week history of severe constipation, abdominal pain and nausea. Bloods: cCa 2.83 mmol/L, PTH 8.3 pmol/L. She was an active and healthy physiotherapist. She had recently become severely depressed and stopped drinking fluids. Dehydration unmasked primary hyperparathyroidism. Calcium remained normal with normal fluid intake, after treatment with Sertraline.
A 66-year old woman presented with delerium. Bloods: cCa 3.37 mmol/L, PTH $<$ 0.3 pmol/L. She had undergone parathyroidectomy 15 years previously and was taking 1-alpha-calcidol and sandocal. She had become increasingly disorientated and emotional over four months but was still self-medicating. CT head revealed brain lymphoma. She had overdosed on her medications secondary to her malignancy. Steroid therapy led to resolution of the lesions.
Discussion
During acute presentations, hypercalcaemia is a common finding. However, it can be the cause of the presentation or an effect of underlying pathology. Its correction is necessary but careful approach of each case is necessary to differentiate between cause and effect and manage appropriately.

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EP032

Systemic Mastocytosis: A Rare but Important Cause of Osteoporosis

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We present a case of a 56 year-old man diagnosed with systemic mastocytosis by the dermatologists on presentation with classical skin lesions, confirmatory bone marrow biopsy and a tryptase level 105 ug/L (NR 2-14). Further genetic testing confirmed KIT D816V mutation. DEXA bone densitometry at diagnosis revealed marked osteoporosis (Lumbar T score -3.7 (Z -3.5), Femoral Neck T score of -2.0 (Z -1.1). He had no history of low trauma fracture and no relevant family history. Other osteoporosis risk factors included alcohol use, smoking history, minimal weight-bearing exercise, previous vitamin D deficiency and SSRI use.

He was treated with calcium and vitamin D supplements and weekly oral bisphosphonate. Due to gastrointestinal side-effects, he was switched to intravenous zoledronate. This has resulted in stabilisation of his osteoporosis on repeat DEXA bone densitometry and no fragility fractures.

The finding of osteoporosis in young men or pre-menopausal women must direct the clinician to carefully exclude any secondary causes of osteoporosis. Systemic mastocytosis is a rare but important cause and requires a partnership with dermatologists. It comprises a heterogenous group of mast cell proliferation disorders, with infiltration of multiple organs including skin and bone. The precise pathophysiology of osteoporosis in systemic mastocytosis is poorly understood but bone involvement is common with osteoporosis being the most common manifestation. The risk of osteoporotic fractures is high especially in men. Furthermore, back pain secondary to osteoporotic fracture may be the only presenting symptom in systemic mastocytosis.

This case highlights the need to consider systemic mastocystosis as a cause of osteoporosis especially in younger men and pre-menopausal women with or without associated skin lesions. Treatment with bisphosphonates remain the first-line treatment for mastocytosis-related osteoporosis and close liaison with dermatologists is advised.

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EP033

Vitamin D Toxicity & Undetectable Serum Levels – A Conundrum

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59 year old woman with relapsing remitting multiple sclerosis (MS), not under Neurology follow-up was privately consulting a nutritionist based in Ireland and following the Coimbra protocol[1] since December 2016. This included colecalciferol (1000-170000 IU/ day), vitamin B-complex and trace elements. Dose adjustments were advised during weekly skype consultations based on blood tests (via General Practitioner) and symptoms.

Fluid intake was 2litres/day ('prescribed' 3-4) for a week when hospital admission was advised for hypercalcaemia (corrected calcium level was 3.76 [2.20-2.60]) and acute kidney injury (AKI) stage1. She was getting thirstier and constipated. Serum 25-hydroxy vitamin D (25-OHD) was reportedly $<$ 15 nmol/L, and parathyroid hormone (PTH) was unsuppressed (4.7 pmol/L [1.6-7.5]). Vitamin D metabolites were requested and sample sent to another laboratory to confirm results by liquid chromatography-mass spectrometry (LC-MS). In view of undetectable 25-OHD computed tomography of chest, abdomen and pelvis was done (adrenal incidentaloma). Rehydration with intravenous normal saline, stopping supplements, led to corrected calcium settling to 2.68 and resolution of AKI.

We advised discontinuation of high dose vitamin D but she attributed significant improvement in her MS symptoms to it. After patient's discharge, it emerged that there was a reporting error (information and technology issue) and the true 25-OHD level in-house was $>$ 374 by immunoassay, and 862 (99.6% vitamin D3) by LC-MS.

Learning points

- Hypercalcaemia secondary to hypervitaminosis D is not widely recognised or reported.
- PTH may be normal in 'gradual' colecalciferol toxicity, even in presence of hypercalcaemia, unlike in 1,25 dihydroxy Vitamin D toxicity e.g. alfacalcidol which happens rapidly
- Patients' faith in their alternative 'treatment', details of which must be sought, may be undeterred despite severe adverse effects.
- Close liaison with chemical pathology colleagues can help solve an apparent clinical conundrum.

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EP034

A rare case of combined hyperparathyroidism and thymoma

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A 67-year-old lady, previously fit and well, presented with chest pain. She denied gastrointestinal or urological symptoms. There was no history of depression, psychosis, previous hip fracture or steroid use. She had regular menstrual cycles until hysterectomy at 50 years of age. She doesn't smoke or drink alcohol. Her mother and father had oesophageal and lung cancer respectively with no family history of hypercalcemia. On examination, she was normotensive with BMI 23.3 kg/m^2. Blood investigations revealed incidental hypercalcemia with elevated parathyroid harmone (PTH) levels. Routine bloods including FBC, TSH, renal function were normal with eGFR of 88 ml/min/1.73 m$^{2.}$ Coeliac and myeloma screen were negative and Vitamin D level was 66.8 nmol/l. DEXA scan confirmed severe osteoporosis and she was started on weekly alendronate. Chest X-ray showed mediastinal widening; CT chest showed a cystic mediastinal mass. Parathyroid SPECT CT showed MIBI avid lesion in anterior mediastinum but no discernible parathyroid adenoma in the neck. Video-assisted thoracoscopic surgery (VATS) biopsy of mediastinal mass was inconclusive. Her mediastinal mass was subsequently removed at thoracotomy. Excision biopsy confirmed evidence of thymoma (Type B1), but no evidence of parathyroid tissue. In the interim, she was treated for breast carcinoma with wide local excision and radiotherapy. Her pre and post-operative corrected serum calcium and PTH values are shown in Table 1. We report a case of thymoma presenting with hypercalcemia, osteoporosis and hyperparathyroidism. Histology confirmed thymoma with a possible ectopic PTH production. Post-operative PTH levels normalised initially but then started increasing, even though serum calcium levels remained normal. This raised PTH could be secondary to bisphosphonates but surprisingly PTH values were normal during immediate post-operative period. Also interestingly, she did not exhibit any signs or symptoms of myasthenia gravis.

	Pre-operative							Post-operative		
	June 2016	Aug	Sept	Oct	Nov	Dec	Jan 2017	Feb	March	June
Corrected serum calcium (2.2–2.6 mmol/l)	2.8	2.9	2.9	2.7	2.9	2.8	3.0	2.47	2.58	2.43
PTH (1.5–7.6 pmol/l)	21.7	14.1	17.2	22	27.7	18.9		4.9	4.6	11.3

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EP035

Parathyroid Perils: Efficiently Investigating Hypercalcaemia for Malignancy

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A 69 year old man presented to hospital with acute hypercalcaemia and renal failure. History included nephrectomy for a benign renal tumour and thyroidectomy for thyroid carcinoma. Presentation adjusted calcium was 2.70 mmol/L with an incompletely suppressed parathyroid hormone level of 0.6 pmol/L. The hypercalcaemia was resistant to both intravenous fluids and bisphosphonates, rising to 3.20 mmol/L. Given his previous cancer, hypercalcaemia of malignancy was strongly suspected. Result of PTH-rp level returned as $<$1.0 pmol/L over 6 weeks later. CT scan demonstrated splenomegaly and small volume lymphadenopathy. Axillary lymph node biopsy done from metabolically active lymph node on PET scan demonstrated CD20 negative angioimmunoblastic lymphoma, which was treated successfully with chemotherapy.

Incompletely suppressed parathyroid level in the context of hypercalcaemia is difficult to interpret. The leading cause of hypercalcaemia in the inpatient setting is malignancy. Malignancies are typically associated with an elevated PTH-rp. Importantly lymphoma can present with hypercalcaemia and either a normal or elevated PTH-rp.
This case demonstrates that whilst PTH-rp level has a role in investigating hypercalcaemia with incompletely suppressed PTH, its use may be limited. The complex preparation of PTH-rp samples is critical for accurate analysis, requiring strict temperature control and decanted containers. PTH-rp sampling often incorporates significant delays through rejected samples and complex laboratory processing. In the context of malignancy, such delays can prove harmful in promptly managing mitotic disease. Furthermore, lymphoma can drive hypercalcaemia through PTH-rp independent mechanisms, both through direct bone effects or 1,25-dihydroxyvitamin D production. We argue increased emphasis should be placed on the measurement of 1,25-dihydroxyvitamin D to help reduce delays in diagnosing the aetiology of hypercalcaemia when clinical and radiological picture do not elicit the diagnosis readily.
In summary, this case highlights the importance of efficient hypercalcaemia investigation when malignancy is suspected, it explores optimal PTH-rp sample preparation and the role of 1,25-dihydroxyvitamin D.

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EP036

Intracranial Calcification

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A 58 year-old Polish lady was admitted to hospital after having had two tonic-clonic seizures. She reported a previous history of seizures but had been seizure-free for 10 years. In addition, she reported a 20 year history of hand spasms and perioral paraesthesia. As part of the investigation for seizures while she was living in Poland 10 years ago, CT head had shown bilateral basal ganglia calcification and on this basis she had been diagnosed with Fahr's disease. On admission, Chvostek's and Trousseau's signs were positive and ECG showed a prolonged QT interval. Blood tests were in keeping with primary hypoparathyroidism with an adjusted calcium of 1.18 mmol/L (2.20-2.60), phosphate of 2.19 mmol/L (0.80-1.50), undetectable PTH <0.7 pmol/L (1.6 -6.9) and 25-OH Vitamin D of 50 nmol/L (51-163). CT head showed extensive dense bilateral basal ganglia, thalamic, and cerebellar dentate nucleus calcification. A diagnosis of Fahr's syndrome associated with idiopathic hypoparathyroidism was subsequently made. Initial treatment was with intravenous calcium gluconate followed by oral sandocal and alfacalcidol. At 4-month follow-up, she denied any hand spasms or paraesthesia and had been seizure-free. There were no signs of neuromuscular excitability, and she reported feeling 'better than ever.' Our case highlights the importance of excluding metabolic abnormalities in all patients with basal ganglia calcification and neuro-psychiatric presentation before diagnosing Fahr's disease. In this case, lack of investigation for metabolic abnormalities 10 years ago possibly resulted in a delayed diagnosis and treatment of idiopathic hypoparathyroidism. In addition, treatment of Fahr's syndrome is directed at correcting the specific metabolic abnormality, for example correction of hypocalcaemia, which reduces seizure frequency. In contrast, only symptomatic therapies such as anti-epileptics or anti-psychotics can be used in Fahr's disease. This therefore emphasises the importance of distinguishing between Fahr's disease and Fahr's syndrome as it affects both treatment and prognosis.

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EP037

When remedy becomes toxin-rare cause of hypercalcaemia

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Objective: We present this case to emphasize the need to consider the uncommon causes of hypercalcaemia and the importance of history taking.
Case report
A 79 year old man with multiple sclerosis was admitted with hypercalcaemia of 3.41 mmol/L, a suppressed PTH and AKI. He was investigated for non-PTH mediated hypercalcemia, having a whole host of investigation. He had normal serum ACE, with no radiological evidence of granulomatous disease or malignancy. He had raised free light chains which prompted myeloma investigation.
His hypercalcemia was quite resistant to IV fluids and IV bisphosphonates. Subsequent investigation revealed an exceptionally high vitamin D level of 375 nmol/L and 1,21-hydroxy-vitamin D of 195 pmol/L (43-144 pmol/L) which prompted Endocrinologist involvement only later on in his management, Given his MS, we suspected that he may have been taking high dose vitamin D to help with MS symptoms. His vitamin D levels have been above 200 nmol/L at least since 2013. However, due to delirium with a concomitant UTI, he mis-informed us that he was taking 1000 units of over-the-counter colecalciferol daily. We suggested treatment with steroids which finally improved his calcium and AKI. His latest blood tests show normocalcaemia of 2.46, PTH 2.20, vitamin D 214.4, eGFR 50.
Retrospectively in clinic, he revealed that he had been taking 10,000 units daily of vitamin D for more than 3 years. He had been following the advice of a doctor he had contacted via the internet, who recommended high dose vitamin D to treat MS.
Conclusion
Though primary hyperparathyroidism and malignancy are the commonest causes of hypercalcaemia, less common causes should be considered, and a careful history is helpful in unraveling the underlying cause and avoid unnecessary investigations.

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EP038

'Calcimimetic'' effect of alfacalcidol in a patient with unusual occurrence of familial hypocalciuric hypercalcemia (FHH) and primary hyperparathyroidism - Case Report

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We report the case of a middle age woman with the first presentation in our clinic for recurrence of hypercalcemia following surgery for parathyroid adenoma.
Her personal history was positive for chronic thyroiditis and with long lasting asymptomatic hypercalcemia not exceeding 11 mg /dL for total plasmatic calcium since 2006. In 2011 her hypercalcemia was worsened (maximum level 13.49 mg/dL) and she was diagnosed with primary hyperparathyroidism due to a left inferior parathyroid adenoma. The histopathological report confirmed the parathyroid adenoma with clear cell and scarce cytoplasm.
Her brother was known as papillary thyroid carcinoma and intermittent hypercalcemia with inappropriate PTH value when tested.
After a six months trial of alfacalcidol, our patient normalizes urinary excretion of total calcium with the maintenance of minimally raised total calcium and PTH in the low reference values.
The unusual occurrence of both familial hypocalciuric hypercalcemia (FHH) and primary hyperparathyroidism in the same patient is reported in literature along with the mutation responsible for the defect. Decreased expression or function of the CaSR may play a pathogenic role in the proliferation of parathyroid cells and can explain the development of parathyroid adenomas. Close monitoring of affected family members over time will provide more information in this regard. Surgical intervention for concomitant primary hyperparathyroidism in FHH patients does not resolve hypercalcemia but is beneficial reducing the degree of hypercalcemia, alleviating the symptoms, and preventing potential complications of hyperparathyroidism.

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EP039

Sclerotic Bone Metastases Diagnosed on DXA

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Case History
A 79 year old gentleman sustained a traumatic fracture of his left humerus in November 2016. Given his age and non-union of fracture, he was referred for a dual X-ray absorptiometry (DXA) scan in May 2017. This demonstrated markedly elevated bone mineral density (BMD) and subsequent investigation was performed. The patient has a past medical history of type 2 diabetes mellitus, hypertension, asthma and kidney stones. He was started on finasteride in 2011, presumably for treatment of prostatic symptoms.
Investigations and Method
The patient attended for DXA scan which demonstrated markedly elevated T-score of 6.6 in lumbar spine 2-4 as well as hip T-score of 2.5. On review of his plain X-rays, he appeared to have multiple sclerotic lesions around the left humerus site. In light of his results, his prostate specific antigen (PSA) was checked and a nuclear medicine bone scan as well as a whole body scan.
Results and Treatment
PSA came back at 1478.5 and alkaline phosphatase was also significantly raised. His isotope bone scan revealed significant uptake in his axial, appendicular skeleton and facial bones which was concordant for his whole body scan.
Conclusion and Points for Discussion
The results are in line with a diagnosis of metastatic prostate cancer. An interesting point about this case was the route of diagnosis. Unfortunately, the sclerotic bone lesions identified on this patient's admission x-rays were missed and it was in fact interpretation of the DXA scan that identified the bony metastases. Ideally, the lesions would have been identified along with the fracture of the humerus, and if this was the case the patient would have had the same line of investigations as above, but significantly earlier.

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EP040

Case report on symptomatic hypocalcemia associated with acute severe malaria - need for vigilance

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A 25 year-old female Polytechnic student who presented at the emergency department with a 5-day history of high grade fever with chills and rigor, headache, generalized body weakness, postpandrial vomiting, epigastic pain and passage of melena and feeling of cramps in her hands and feet. Had no history of PUD but had used NSAIDS for pains and the cramps.
Her RBS was 155 mg/dl. Genotype unknown. LMP 6/4/17
Physical examination showed an acutely ill-looking lady, febrile (39.2°C), with demonstrable carpopedal spasms, not pale, anicteric, and had no pedal edema
Her pulse was irregular, of normal volume and the rate was 84/minute. The BP was 133/103 mmHg. Other systems were okay
She was treated as a case of acute severe malaria with hypocalcemic tetany and Upper GI Bleeding
She got better with 10% calcium gluconate infusion, anti-malarial and parenteral rabeprazole and her BP was 111/81 mmHg by next day. She was discharged after 5 days to the MOPD for follow up, on oral calcium supplements and rabeprazole
RESULTS
Total calcium – 1.37 (2.1 -–2.5)mmol/L (at admission)
Albumin – 30.05 (35 - 50)g/L
Magnesium – 0.86 (0.7 - 1.15)mmol/L
Phosphate – 1.89 (1.0 - 1.5)mmol/L
Total Calcium – 1.8 (2.1 - 2.5)mmol/L (next day after Ca gluconate infusion)
Total Calcium – 2.16 (2.1 - 2.6)mmol/L (5^{th} Day Of Admission [DOA])
Corrected calcium – 2.34 (2.1 - 2.6)mmol/L (5^{th} DOA)
Phosphate – 0.97 (0.8 - 1.4)mmol/L (5^{th} DOA)
The serum PTH urea, creatinine, electrolytes, CBC, TFT were normal. Serum vitamin D3 and calcitonin not done.
Abdominal and Neck USS – No parathyroid enlargement or abnormal abdominal findings
ECG findings – Sinus rhythm, atrial premature complexes, prolonged QTc

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Clinical Biochemistry

EP041

Sertraline-induced non-hyperinsulinemic hypoglycaemia in a non-diabetic patient : A case report

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Case
A 44-year-old patient presented with symptoms of sweating, shaking and hunger, which were all eased by eating. Her symptoms were suggestive of hypoglycaemia, experienced predominantly 2-3 hours after meals. Hypoglycaemia was confirmed during these episodes. She had normal liver and renal function. There was no history of Diabetes Mellitus.
Her symptoms improved slightly with measures of adjusting her diet but did not settle completely. She also complained of lethargy, weight loss, and skin changes. We arranged 72 hours supervised fast, as well as a short synacthen test to rule out both the possibility of insulinoma and adrenal insufficiency.
72-hour fasting results revealed that she had insulin independent cause for hypoglycaemia. Her venous glucose was 2 mmol/L, ketones $>$ 5000 mcg/L, C-peptide $<$ 94 pmol/L and serum insulin was 12 pmol/L. Sulphonylurea screen was negative. The short synacthen test showed normal cortisol response of 352 nmol/L at 0 minutes and 660 nmol/L at 30 minutes.
She was on sertraline for depression and due to its potential side effect of hypoglycaemia, we stopped the drug, after exclusion of all other causes for the hypoglycaemia. Her symptoms completely resolved when she was weaned off Sertraline.
Discussion
Although the exact mechanism of hypoglycaemia caused by Sertraline is not known but it has been shown to blunt postprandial hyperglycemia in rats and to potentiate the hypoglycemic effects of sulfonylurea agents in humans. It is not been reported to cause hypoglycemia independently but in this patient hypoglycaemic episodes were resolved after discontinuation of sertraline.
Conclusion
Prescription of SSRIs is common and due to to the potential side effect of hypoglycemia associated with these drugs, SSRI usage should be considered when assessing patients for hypoglycaemia.

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EP042

A rare cause of acute severe hyponatraemia secondary to the syndrome of inappropraite anti-diuretic hormone (SIADH) secretion

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Hyponatremia is the commonest electrolyte abnormality presenting to Medical Admissions and when acute, severe and symptomatic, is associated with high mortality. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the most common underlying disorder in hospitalised patients with euvolaemic hyponatraemia and is a complication of many clinical conditions and drug therapies.
We discuss the cases of two patients presenting with acute severe hyponatraemia secondary to SIADH, admitted to the same hospital within a 2-week period. Patient 1 presented with severe abdominal pain and hypertension and was initially investigated for a pelvic mass. Serum sodium was normal on admission but dropped 11 mmol/L in 8 hours, precipitating a seizure. She was admitted to the intensive treatment unit (ITU) for close monitoring. Patient 2 presented with increasing confusion, lethargy and abdominal pain. Her admission sodium was 108 mmol/L. She had a seizure in the emergency department and was intubated and transferred to ITU.
Both patients received several boluses of 2.7% hypertonic saline and, showing biochemistry consistent with SIADH, were fluid restricted to 750 mls daily. Extensive imaging in each case failed to identify an underlying cause. The combination of unexplained SIADH, hypertension and abdominal pain raised the possibility of porphyria as a unifying diagnosis. This was confirmed by the presence of elevated urinary porphobilinogen and total porphyrin concentration in both patients. They were commenced on IV haem arginate leading to normalisation of sodium levels.
Acute intermittent porphyria (AIP) results from partial deficiency of porphobilinogen deaminase activity. Clinical manifestations include recurrent abdominal pain, peripheral neuropathy and neuropsychiatric symptoms. Hyponatraemia occurs in approximately 20% of cases of symptomatic AIP.

The number of possible causes of SIADH is extensive and maybe difficult to determine despite thorough investigation. We discuss the importance of considering rarer causes for unexplained hyponatraemia in those with additional symptoms suggestive of underlying pathology.

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EP043

A Case of Hypoglycaemia

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We present this 62-year-old man with a background of Marfan's Syndrome, aortic valve replacement, atrial fibrillation and asthma who presented with increasingly severe episodic hypoglycaemia over a period of 22 years. Of note he was not diabetic and was not on any hypoglycaemia-inducing medications. Extensive investigations included the following: 72 hr fast, 5 hr OGTT, continuous glucose monitoring, basic biochemistry, hormone profiles (GH, LH, FSH, testosterone, TFTs, ACTH, SST, cortisol, GH, IGF-1, urinary metanephrines), insulin/c-peptide, screening for inherited metabolic conditions and imaging of his pancreas. Their sole abnormal finding was of significant reactive hypoglycaemia with a plasma glucose level of 2.4 mmol/L at 2.5 hours following a 75 g glucose load. Abdominal ultrasound, abdominal CT scanning and endoscopic ultrasound did not reveal any abnormalities in the pancreas, liver or kidney. A diagnosis of Non-Insulinoma Pancreatogenous Hypoglycaemia Syndrome (NIPHS) was made. Various treatment regimens were implemented including low GI diet, acarbose with some beneficial effects, and later a GLP1 inhibitor with more limited success. Octreotide 50 mcg QDS subcutaneously produced a dramatic decrease in frequency of hypoglycaemia but tachyphylaxis developed despite a dose increase to 100 mcg QDS. Currently he is being treated with a regimen of diazoxide 100 mg tds and prednisolone 20 mg once daily with significant improvement in the number of episodes but with side effects including symptomatic postural hypotension. This case highlights a rare but increasingly recognised form of hypoglycaemia that can be very difficult to treat.

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EP044

Investigating an isolated serum alkaline phosphatase: an incidental mediastinal seminoma

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Serum alkaline phophatase (ALP) may be released from various sources, including liver, bone, thyroid, intestine and placenta. Herein, we describe a rare case of an isolated serum ALP rise initially dismissed, and later resulting in an incidental finding of a mediastinal seminoma.

A 56-year-old gentleman was referred to the Endocrinology Outpatients by his general practitioner, with a 1-month history of presumed post-viral fatigue and rise in serum ALP. He was initially investigated by the Gastroenterologists for two benign liver cysts, with no interval change on imaging. The patient was thereafter discharged.

Subsequent endocrine investigations revealed mildly low Vitamin-D at 55 nmol/L, ESR 45 mm/hour, IgG 17.2 g/dL and IgM 2.45 g/dL with slight polyclonal increase in gamma region. Autoimmune, thyroid and pituitary profile normal. A further rising ALP prompted a skeletal survey, which showed no bony lesions, but an anterior mediastinal mass 15.6 cm×8.6 cm x14 cm encasing at least two-thirds of the circumference of the ascending aorta. No other significant lesions were found on staging CT. Diagnostic core biopsy was in keeping with a seminoma, associated with strongly, diffuse positive placental ALP (PLAP), and positive CD5 and CD45.

Differential diagnosis of a mediastinal mass in the context of an isolated ALP rise, include thymoma, lymphoma and teratoma. Less than 5-7% of germ cell tumours are extragonadal, but often respond well to radio/chemo-therapy. The patient in our case underwent neoadjuvant chemotherapy and surgery, remaining disease free thereafter. Prompt diagnosis is therefore paramount to minimise complications.

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EP045

A curious case of recurrent episodes of multiple-electrolytes derangement

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Introduction

Single-electrolyte derangement is a common biochemical finding. Multiple-electrolytes derangement is less common and require multiple and simultaneous corrective therapies. We present a patient who had multiple admissions with multiple-electrolytes derangement, which after further evaluation required a single therapeutic intervention.

Case

A 26-year-old lady had eight admissions over three years with abdominal pain and vomiting. During each admission she had life-threatening hyponatraemia, hypokalaemia, hypomagnesaemia, hypochloraemia, hypo-osmolality, and low serum urea and creatinine values. She was also being investigated for a 4-year history of abdominal pain, cyclical vomiting with chronic hypokalaemia and hypochloraemia. Conditions such as carcinoid syndrome, acute porphyria, celiac disease, adrenal dysfunction, intestinal polyps and other intra-abdominal pathologies had been ruled out.

Investigation and management

We suspected excessive fluid intake, which she denied. We assessed her serum and urine electrolytes before and after a 12-h fluid fast. The results (Table 1) were indicated water intoxication (potomania) as levels normalised soon after a fluid-fast. The patient later admitted drinking 3–5 l of water daily to relieve abdominal discomfort but during episodes of abdominal pain would drink more than 6 l in one sitting before presenting to the Emergency Department. An explanation of water-intoxication and patient-counseling resulted in only mild vomiting-related electrolyte derangement on subsequent admissions.

Conclusion

We have presented a case of multiple-electrolytes derangement due to chronic and acute water intoxication. If left unchecked, this condition can be associated with serious neurological sequelae. Early detection, explanation and patient counseling are required to prevent further harm.

Table 1 Serum and urine electrolyte values before and after the 12-h fluid fast test

Chemical test	Reference range	Results before the test	Results after the test
Serum sodium	133–146 mmol/l	132	143
Serum potassium	3.5–5.3 mmol/l	3.4	4.8
Serum chloride	95–108 mmol/l	94	102
Serum urea	2.5–7.8 mmol/l	1.4	2.5
Serum creatinine	50–120 μmol/l	47	62
Serum osmolality	275–295 mOsm/kg	259	282
Urine sodium		23	22
Urine potassium		15	53
Urine osmolality	300–110 mOsm/kg	112	286

*Known to have chronically low serum potassium, chloride and urea levels

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EP046

Blood glucose control in a pregnant female with Type 1 diabetes and Medium-chain acyl-CoA dehydrogenase deficiency (MCADD)

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Background

Medium-chain acyl-CoA dehydrogenase deficiency (MCADD) is an autosomal recessive inherited disorder resulting in the inability to breakdown medium-chain fatty acids to provide energy during periods of low-calorie intake and hypoglycaemia (infections, fasting, vomiting). Without urgent treatment, the accumulation of toxic fatty acids leads to encephalopathy and sudden death.

Pregnant females with Type 1 diabetes require strict glucose control for a favourable outcome for mother and baby. National guidelines advise aiming for fasting capillary blood glucose (CBG) levels

Case

A 17-year-old lady was diagnosed with MCADD soon after birth and Type 1 diabetes at age 7 years. She had paediatric/metabolic disease specialist care thought her childhood and kept her CBG levels raised to avoid hypoglycaemia [median (range) HbA1c: 89 (68-129) mmol/mol over the past 3 years]. She attended our adult diabetes-antenatal clinic during her pregnancy.

Management

With 1-2 weekly clinic visits she continued her basal-bolus insulin regimen (Lantus & Novorapid), Folic acid and Aspirin. She improved her CBG levels throughout pregnancy: median (range) HbA1c: 53 (42-55) mmol/mol. During labour and delivery we used a variable rate insulin and glucose infusion, aiming for CBG levels between 5-10 mmol/l rather than the usual 4-7.8 mmol/l, so as to maintain sufficient glucose-related energy and block alternative energy-producing pathways. She had an uncomplicated delivery.

Conclusion

The combination of Type 1 diabetes and MCADD in pregnancy is a rare challenge to the obstetrician, diabetologist, dietitian and most importantly, to the patient. Uncomplicated cases (with no concurrent illness, frequent vomiting or prolonged fasting) should go well. The importance of a multidisciplinary team approach to care and seeking advice from the inherited metabolic disease specialist cannot be overemphasized.

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EP047

A rare metabolic condition presenting to Ophthalmology

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Homocystinuria is a rare autosomal recessive disorder of the transsulfuration or methylation pathway in methionine metabolism.

We present a case of a 25 years old female, who presented with rapid onset loss of vision in both eyes and short-sightedness. She had a background of well-controlled epilepsy, normal mental and physical development. She had no family history of Marfan's syndrome.

On examination, systemic review was unremarkable and she was clinically euthyroid. She had high arched palate with no other stigmata of Marfan's syndrome. Ocular examination revealed inferior nasal subluxation of her lens bilaterally with zonule dehiscence.

Routine haematology and biochemistry indices were normal. Vitamin B concentration was 152 ng/L (191-663 ng/L). Urine homocysteine concentration was 524.5 umol/L (2.0-14.2 umol/L), and plasma homocysteine concentration measured on two occasions was 237.9 umol/L and 254.5 umol/L (0-16.0 umol/L) respectively. Genetic test confirmed a heterozygous pathogenic mutation on the cystathionine B synthase (CBS) gene c.833T>C; p1278T. ECG and Echo were normal. CT angiogram revealed normal aortic root dimensions.

Low protein diet was recommended. She was commenced on Pyridoxine 100 mg TDS. Folic acid and Vitamin B12 were supplemented. She was treated with bilateral vitrectomy and lensectomy with right intra-ocular lens implant. Increased risk of thromboembolism was also discussed and managed appropriately.

Although visual disturbances have been described as a complication in more common metabolic problems such as Thyroid Eye Disease, it is worth remembering rare metabolic causes in patients presenting with visual problems. Prompt diagnosis and management of a homocystinuria can reduce the risk of thromboembolic stroke in the young (<30 years).

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EP048

Pre-eclampsia as a rare cause of severe hyponatraemia

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Background

Hyponatraemia is the commonest electrolyte abnormality. It carries a mortality rate of above 50% when plasma sodium concentration falls below 115 mmol/L. We present a case of severe hyponatraemia complicating pre-eclampsia in a primiparous woman.

Case Report

A 23-year old healthy primigravida was admitted at 34 weeks' gestation following an episode of reduced foetal movements. She was hypertensive (BP 171/98 mmHg) and had 2+ proteinuria. Her sodium level was 133 mmol/L (Normal Range, NR: 135-145 mmol/L) and urine protein-creatinine ratio was 229 mg/mmol (NR: 0-15). Cardiotocography was unremarkable. She was diagnosed with pre-eclampsia (PET) and started on labetalol.

Serum sodium level dropped to 126 mmol/L and two days later, reached a nadir of 114 mmol/L – she developed marked oedema. Further investigations: serum osmolality 255 mOsm/kg (NR: 275-290 mmol/L); urine osmolality 445 mOsm/kg; urine sodium <10 mmol/L; normal thyroid function. Isotonic sodium chloride was carefully administered. She was delivered by caesarean section at 36+1 weeks because of persistent hyponatraemia and worsening symptoms of pre-eclampsia, including suspected acute fatty liver (ALT 1348 iu/L; NR <40 iu/L). A male infant was born (Apgar score 9 at 10 minutes) – he had mild hyponatraemia – corrected by the paediatricians. Within 24 hours of delivery, maternal hyponatraemia had improved to 133 mmol/L. Recovery was complicated by intrapartum sepsis. She was discharged eight days later with normal BP.

Discussion

Pregnancy involves physiological changes affecting water and sodium homeostasis. However, most women with PET do not develop hyponatraemia. We postulate that this was a case of hyponatraemia with hypervolaemia (excess extracellular sodium and total body water) as a result of impaired free water clearance secondary to pre-eclampsia. SIADH was discounted because of low urinary sodium and oedema.

We draw attention to severe hyponatraemia as a rare indication for urgent delivery in pre-eclampsia. This requires multidisciplinary management and continuing postpartum care to ensure favourable maternal/ neonatal outcomes.

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EP049

'2' much of a problem with hypoglycaemia

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Background

An 88 year old gentleman was referred to the endocrine team as an inpatient with recurrent episodes of spontaneous hypoglycaemia. These occurred in the early hours of the morning when he was found to be unrousable from sleep. There was no background history of diabetes. He was under the oncology team on this admission with pyrexia post-palliative chemotherapy with trabecitidine. Significant past medical history include metastatic solitary fibrous tumour of pelvis, bilateral hydronephrosis, stage 3B chronic kidney disease and congestive cardiac failure.

Investigations

Capillary blood glucose (CBG) was between 1.2 and 3.2 on 3 consecutive nights prior to endocrine review (daytime readings 4.1 – 8.2). Venous bloods were requested the following night during hypoglycaemia and the results were (normal range in parantheses): plasma glucose 2.2 mmol/l (3.5-11), insulin <10 pmol/l, C-peptide 380 pmol/l, sulphonylurea negative, IGF-I 7.1 nmol/l (4.6 – 23.4), IGF-II 137.2 nmol/l, IGF-II:IGF-1 ratio 19.3 (<10).

Management

Since the patient was for palliative care only, prednisolone 10 mg BD was started to avoid symptomatic hypoglycaemia, which was reduced to 5 mg BD before discharge. CBG remained from 6.5 – 10 following this, including nocturnally, and he was discharge home.

Discussion

Tumours of mesenchymal and epithelial origin (eg. fibroma, fibrosarcomas and hepatomas) can produce IGF-II which causes fasting hypoglycaemia similar to insulin-producing islet-cell tumours. Characteristically, insulin, C-peptide, IGF-I and growth hormone levels are normal or low in the presence of hypoglycaemia. Surgical resection of the tumour, where possible, can produce a cure. However in this instance we opted for symptomatic treatment with steroids to good effect.

Conclusion

In patients presenting with spontaneous hypoglycaemia with a background of fibrosarcoma tumours (particularly if they retroperitoneal or pelvic), it is important to consider IGF-II secretion as a paraneoplastic syndrome

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EP050

Starvation ketoacidosis – a rare but significant metabolic condition

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Diabetic ketoacidosis and pregnancy related ketoacidosis are the most common forms of ketoacidosis seen in acute medical units. We describe here two rare cases of starvation ketoacidosis.

Case 1: 63 years old gentleman with no history of diabetes, presented with persistent vomiting for 48 hours. His admission bloods revealed Serum Bicarbonate of 8, pH 7.19, pCO2 2.7, base excess of -17.8, plasma glucose 5.2 mmol/l and serum alcohol <100. Serum ketones were 3.4 mmol/l. He was managed with iv fluids mainly with dextrose infusions. His symptoms, serum ketones and pH levels normalised while his blood glucose remained stable over 3 days and was discharged home.

Case 2: 67 years lady with past history of COPD, excess alcohol intake and osteoporosis, presented with feeling unwell, since she stopped eating after she had an argument with her son 5 days ago. Her bloods revealed Serum Bicarbonate of 14, pH 7.43, pCO2 3.5, base excess of -4.7, plasma glucose 6.7 mmol/l and serum alcohol <100. Serum ketones were 3.4 mmol/l. She was managed with iv fluids mainly with dextrose infusions with iv Vitamin B complex. Her symptoms, serum ketones and pH levels normalised while her blood glucose remained stable over next day and was discharged home.

These two cases highlight the condition of starvation ketoacidosis, being a significant cause of metabolic acidosis, presented with symptoms of vomiting and being unwell respectively. Prompt diagnosis and treatment targeted to correct volume and calorie (mainly from carbohydrates) deficit helped to move these patients from a metabolic state based on fatty acid catabolism to eumetabolic state. Distinction from diabetic keto-acidosis is extremely important. If misdiagnosed as euglycaemic diabetic ketoacidosis, consequent inappropriate insulin therapy would lead to hypoglycaemia in an already carbohydrate depleted individual.

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EP051

Primum Non Nocere – the need for appropriate assessment before starting testosterone therapy

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A 41 year old Emirati man was reviewed in January 2016 for hypercholesterolaemia managed on diet alone, but direct questioning revealed gradual onset erectile dysfunction over 2 years, treated by a urologist elsewhere. Initial response to Cialis had waned over 18 months. Testosterone replacement (Nebido) had been initiated in June 2015 on the basis of one low morning total testosterone of 3.89 nmol/L (normal range 8.64 – 29). SHBG and prolactin were normal. No other investigations had been carried out. There had been no symptomatic improvement despite treatment for 8 months with total testosterone now normal at 11.26 nmol/l.

He had left sided limb weakness following childhood poliomyelitis but no potential cause for hypogonadism. Examination including visual fields was otherwise unremarkable.

Pituitary axis testing demonstrated low random cortisol but appropriate response to short synacthen testing. Gonadotrophins were suppressed as expected. Haematocrit was upper end of normal at 0.500 L/l (0.38-0.51) and haemoglobin 168 g/l (126-177)l, suggesting developing testosterone-induced polycythaemia. PSA was normal. Ultrasound of testes showed bilateral hydrocoeles but nothing else significant. DEXA revealed left femoral neck osteoporosis attributed to disuse atrophy. Treatment with Alendronate was commenced.

Discontinuing Cialis caused worsening of erectile dysfunction after 2 weeks despite adequate serum testosterone, and was restarted. Stopping Nebido had no impact on symptoms. Subsequent monthly measurements demonstrated a rise in LH and FSH levels to normal. Although serum testosterone remained low (nadir 4.29 nmol/l with Free Androgen Index 18.9% at 3 months) FAI normalised at six months. Haemoglobin is now 146 with haemotocrit 0.441 and he remains symptom free on Cialis.

Total testosterone levels alone have a poor specificity in the diagnosis of testosterone deficiency. The results should be interpreted together with an SHBG (and a calculated FAI), LH and FSH. Trials of testosterone may have a placebo effect and suppress gonadotrophins. Withdrawal of inappropriate testosterone therapy can then result in a low testosterone for several months.

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Diabetes and Cardiovascular

EP053

Hypoglycaemia manifested as transient cardiac arrhythmias in a non-diabetic: a case report

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Background

Hypoglycaemia is a life-threatening condition commonly encountered in emergency department (ED), mainly among individuals with diabetes on insulin or oral hypoglycaemic agents (OHA). Hypoglycaemia in non-diabetic individuals is not a common condition and its often a diagnostic challenge for clinicians especially when presented in an unusual way. Although it does not seem to be a cardiac emergency feature, various electrocardiographic manifestations due to hypoglycaemia have been reported.

Case

Here, we report the case of a 49-year-old man who presented because of feeling of fatigue, 'impending death', and dizziness of about 30 minutes before presentation. He was observing Ramadan fast and his last meal was about 12 hours earlier. The urgent ECG showed sinus tachycardia, ST segment elevation and right bundle branch block (RBBB), and a blood glucose of 2.5 mmol/l (45 mg/dl). All these cardiac arrhythmias promptly reverted to sinus rhythm shortly after correction of hypoglycaemia with 10% dextrose infusion. Hence, the precipitating event for these ECG findings was thought to be due to hypoglycaemia. Although, the patient was a known hypertensive on medications, a review of previous ECGs did not reveal any arrhythmias. Also, all subsequent serial ECGs done during the admission were all normal and repeated cardiac markers all normal.

In conclusion, clinicians should be aware of unusual clinical presentations of hypoglycaemia including cardiac arrhythmias for which 'medical cardioversion' can simply be made with dextrose infusion to correct hypoglycaemia. Hence, a routine bedside blood glucose estimation may be indicated in such situation in the ED.

Keys: Cardiac arrhythmias, ECG, Hypoglycaemia, Non-diabetic

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EP054

Significant improvement in response to the GLP1-agonist 'Liraglutide' following change in injection site

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Variability in treatment response with respect to GLP1 agents is well-accepted but incompletely understood. In a specialist GLP-1 clinic at UHCW, we describe a case of improved therapeutic response following change in injection site. Currently, advice is injection in the abdomen or thigh.

A 61 year old man was commenced on Liraglutide 1.2 mg subcutaneous OD injection, in 2013. Previously managed with glimepiride 4 mg and metformin 1 g BD, with suboptimal HbA1c of 93 mmol/mol, weight 111.4 kg.

After 2.5 years, HbA1c fell to 67 mmol/mol, weight of 111.2 kg (stable). Having previously responded, by 3 years of therapy his HbA1c began climbing to 74 mmol/mol. Weight remained stable, at 111.8 kg. At 3.25 years of therapy, he reported self-initiated change in injection site over two weeks prior to clinic. Having made no change to his diet, and previously injecting in the abdomen, he began injecting the thigh over prior two weeks (self-instigated). He recorded data on a data management system one month prior to, and two weeks after, change in site.

Over two weeks, he noted a dramatic response. FBG dropped from an average of 8.5 to 5.5 mmol/L. Average post-breakfast glucose fell from 12.2 to 9.4 mmol/L; post-lunch glucose dropped from 8.9 to 6.2 mmol/L; post-evening meal fell from 9.3 to 7.6 mmol/L, fall in pre-bed glucose from 8.9 to 6.7 mmol/L. HbA1c also fell to 55 mmol/mol. Having been static previously at 118 cm, his waist circumference also dropped to 113 cm, with concurrent reduction in weight to 106.6 kg.

At 4 years, HbA1c was 39 mmol/mol, (drop of 35 mmol/mol drop since injection site change); weight reduction of 13.6 kg to 98.2 kg in same time period. Glimepiride was 2 mg, down from 4 mg. To our knowledge, such a significant improvement based on injection site has not been described.

This case highlights, therefore, anecdotal evidence suggesting site-specific efficacy with relation to liraglutide, and further work should focus on this and its potential mechanisms, including site-specific differences in absorption.

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EP055

Diabetes presenting as spontaneous hypoglycemia. Is it possible?

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Diabetes can manifest not only with hyperglycemia,but also as hypoglycemia. It typically occurs postprandially,3-5 hrs after meals and is preceded by early post meals hyperglycemia.

58 yrs old Saudi gentleman had Type 2 diabetes for 5 yrs,dyslipidemia,Mitral valve disease,Bronchial asthma, GERD,vitamin D deficiency,BPH and depressive illness. He had presented to the outpatient Diabetes clinic in November, 2015 with post-prandial hypoglycemia 2-3 hrs post-meals esp. lunch & supper (with sympathetic symptoms and Whipple's triad). He denied any neurological symptoms. The minimum recorded RBS at home was 70 mg/dL. He had intermittent retrosternal burning. His weight & the bowel habits were usual. Rest of the systemic review was unremarkable. His deceased father had diabetes. Our patient was initially on Metformin that was later discontinued. Other medications included Simvastatin, Cholecalciferol, Mebeverine, Pantoprazole, Fluoxetine, Symbicorte inhaler and Ibuprofen.

He was fully alert, oriented and co-operative. Vitals were preserved. BMI 28.09 kg/m^2. There was Lt hallux valgus deformity. CVS examination revealed a Grade 1,non-radiating systolic murmur in the mitral area. Rest of the general & systemic exam was unremarkable.

The complete blood count, ESR, liver and renal parameters were well within normal limits. Bone profile, Vitamin D,PTH were normal. HbA1c was 42 mols/mols IFCC. Serum testosterone,LH,FSH,Prolactin,PSA,C-peptide and insulin levels were normal. Echocardiogram showed mitral valve prolapse and mild MR. U/S Abdomen & prostate were normal. Upper GI endoscopy was consistent with gastro-esophageal reflux disease.

His fasting blood glucose was 82 mg/dl. The 75 G oral glucose tolerance test showed an RPG of 220 mg/dl,2 hrs post glucose,that dropped to 65 mg/dl after 3 hrs. The continuous glucose monitoring system for 7 days revealed post-prandial peaks of >250 mg/dl,followed by nadir upto 70 mg/dl.

Our patient was diagnosed to have a reactive hypoglycemia, which can be a feature of Mild Type 2 diabetes. He was referred to the nutritionist,advised avoidance of simple sugars,encouraged to take complex carbohydrates and small, frequent meals. The patient's hypoglycemic episodes got settled with the change in his dietary pattern.

Impaired glucose tolerance and diabetes are the known causes of reactive hypoglycemia,which should always be borne in mind.

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Neoplasia, Cancer and Late Effects

EP057

Cardiac Paraganglioma associated with SDHB mutation and elevated 3-methoxytyramine levels

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Case

We report a rare case of a primary cardiac paraganglioma. A 49-year-old male was found to have elevated3-methoxytyramine (3-MT) levels with normal metanephrines, having undergone a screening test following discovery of SDHB gene mutation, after his 10-year-old niece developed a phaeochromocytoma.

The patient demonstrated no hypertension and did not bear signs of catecholamine excess, but on direct questioning had experienced palpitations. Biochemistry revealed persistently high serum and urine 3-MT (3xULN), and normal adrenaline and nor-metadrenaline metabolites. MRI head and neck and ^{123}I- MIBG scans were normal, whilst CT chest showed indeterminate lung nodules. ^{18}F- FDG-PET scan showed an area of high uptake suggestive of a paraganglioma in the thorax. Cardiac MRI showed a 3.7x2.9 cm lesion in the inter-atrial groove extending superiorly between the junction of the right upper pulmonary vein and left atrium, compressing the superior vena cava. The patient was alpha- and beta blocked in preparation for thoracic surgery.

Progress

Before the planned surgical intervention the patient presented as an emergency with chest pain, requiring urgent cardiac bypass surgery for resection of the cardiac tumour and atrial walls, given intraoperative exploration revealed tumour invasion into interatrial septum.

Discussion

Paragangliomas in the chest are uncommon, accounting for less than 2% of systemic paragangliomas. Primary cardiac paragangliomas are an extremely rare finding. The association between SDH mutations and primary cardiac paraganglioma is reported in the literature, however the anatomical location of interatrial groove in this case is unusual. In this case, the elevated 3-MT level in both plasma and urine was a key finding leading to the diagnosis.

Learning points

- Interatrial groove is a rare anatomical location for a catecholamine excess tumour
- False negative ^{123}I- MIBG is common in extra-adrenal phaeochromocytoma/-paraganglioma associated with SDHB mutations
- Persistent isolated elevation of 3-MT in patients with known high-risk genetic inheritance should prompt comprehensive evaluation.

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EP058

A Novel cause of non-islet cell tumour hypoglycaemia

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Ectopic insulin secreting tumours are rare and infrequent. Presentation can be with recurrent or constant hypoglycaemia often in older patients with advanced cancer. The mechanism is through: insulin or insulin-like activity (IGF-2)(often termed non-islet cell tumour hypoglycaemia), reduced gluconeogenesis, disruption of glucagon metabolism, or utilisation of glucose by the tumour. Neuroendocrine tumours are recognised as having hypoglycaemic potential.

We describe a 73 year old male, presenting as an emergency with confusion and sweats. Pre-hospital glucose was <1 mmol/mol. Following treatment, admission glucose was 1.8 mmol/mol. Past medical history and drug history were unremarkable. Clinical examination revealed a large irregular right upper quadrant mass. Staging CT revealed hepatic, lung and sclerotic bone metastases and a normal pancreas. Liver biopsy was arranged. Biochemistry revealed: a blood glucose of <0.1 mmol/L with inappropriately elevated insulin of 224.3 pmol/L and C-peptide of 1953 pmol/L, and IGF-1 of 25 ug/L. Glycaemia became difficult to manage with oral carbohydrate alone. Prednisolone was initiated at a dose of 40 mg daily, which initially controlled blood glucose. Rapid recurrent hypoglycaemia ensued and IV 10 % dextrose and oral diazoxide were required. Octreotide subcutaneously was also initiated. Tumour markers revealed a prostatic specific antigen levels of 82.7 ng/ml and Chromogranin A 16.5 ng/ml. Degarelix was commenced for presumed prostate adenocarcinoma, but sadly he did not wish for further intervention and withdrew consent for treatment. Liver biopsy revealed a large cell poorly differentiated neuroendocrine carcinoma (NEC).

Post-mortem revealed a liver effaced by multiple deposits with no remaining parenchyma and a normal pancreas and small bowel. Histology revealed a mixed small and non-small cell NEC in the left adrenal metastasis and a large infiltrated prostate containing well and poorly differentiated adenocarcinoma and high grade neuroendocrine small cell carcinoma. This to our knowledge is the first report of ectopic insulin secretion in association with a mixed disseminated high grade neuroendocrine carcinoma of the prostate.

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EP059

Pneumocystis pneumonia in Cushing's syndrome due to ectopic ACTH

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Introduction
Opportunistic infections are a recognised complication of severe hypercortisolism. We report a case of *Pneumocystis* Pneumonia (PCP for formerly named Pneumocystis carinii pneumonia) in patient with ectopic Cushing's syndrome (CS) caused by a metastatic neuroendocrine carcinoma of the lung.
Case history
A 61-year old male attended the Acute Medical Unit for investigation and treatment of severe and recurrent hypokalaemia. His random cortisol at presentation was 1404 nmol/L, ACTH 250 ng/L(normal <50) and 24-h urine free cortisol of 6363 nmol/24 h (upper limit of normal 270). Other cushingoid features included hypertension, easy bruising and central fat distribution. Further endocrine investigation suggested ACTH-dependent hypercortisolism of non-pituitary origin. Whole body CT demonstrated a left upper lobe lung nodule with multiple liver metastases. Liver biopsy and immune-histochemistry confirmed large cell neuroendocrine carcinoma. Following treatment with metyrapone and ketoconazole, the hypokalaemia resolved and hyper-cortisolaemia improved. One week after initiation of treatment the patient developed a cough, temperature and shortness of breath. CT Pulmonary Angiogram showed bilateral upper lobe dense consolidation. Broncho-alveolar lavage revealed *Pneumocystis jirovecii* (formerly PCP) and the patient was treated with trimethoprim and sulfamethoxazole.
Discussion
Similar to our case, PCP has been diagnosed after initiation of cortisol-lowering therapy in the majority of the reported cases in patients with CS. This suggests that immune reconstitution is an important component or even a prerequisite for development of clinically overt PCP in this population. There seems to be a relationship between the degree of hypercortisolism and the susceptibility to opportunistic infections. Our case highlights the fact that patients with severe hypercortisolaemia, more commonly seen in ectopic ACTH syndrome, may be at particular risk of PCP infection following treatment with cortisol-lowering agents. Prophylaxis against *pneumocystis jirovecii* should be considered before starting cortisol-lowering therapy in order to minimise the risk of PCP.

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EP060

A rare case of MEN 4 presenting with hypercalcaemia in a patient with microprolactinoma 6 years after the diagnosis

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Multiple Endocrine Neoplasia is characterised by the occurrence of tumours involving two or more endocrine glands within a single patient. MEN are autosomal dominant disorders. Four forms have been described: MEN 1 due to menin mutations, MEN2 (previously MEN2A) due to mutations of a tyrosine kinase receptor encoded by the rearranged during transfection (RET) protoncogene, MEN3 (previously MEN2B) due to RET mutations and MEN4 due to cyclin-dependent kinase inhibitor (CDNK1B) mutations. Each MEN is associated with the occurrence of specific tumours. MEN4 is characterized by the occurrence of parathyroid and anterior pituitary tumours in association with tumours of the adrenals, kidneys, and reproductive organs.
We are presenting the case of a 31 year old female referred to our Endocrine Clinic by the Fertility Clinic with hyperprolactinaemia (PRL: 1158 mu/L) in March 2010. Her MRI pituitary revealed a microprolactinoma and was started on cabergoline with good response (PRL: 156 mu/L). In August 2016, she came back in Clinic for her routine follow up. Her prolactin levels remained normal but hypercalcaemia (CorrCa: 2.70 mmol/L) was noted. Her PTH was subsequently tested and found to be elevated (9.9 pmol/L) and her Vitamin D levels were normal (79 nmol/L). The results were in keeping with primary hyperparathyroidism. Her MIBI and USS parathyroid didn't reveal any distinct adenoma. The suspicion of MEN was raised and she was referred for genetic testing. Mutation analysis of the AIP, CDKN1B, MEN1 and RET genes was requested. The patient was found to be heterozygous for a novel CDKN1B frameshift mutation consistent with a diagnosis of MEN4.
This case illustrates the required level of clinical suspicion when encountering cases of patients with more than one endocrinopathies in order to refer the appropriate cases for genetic testing. It also underlines that the management of these cases requires multidisciplinary approach and input from various specialities (endocrinologists, clinical geneticists, radiologists, oncologists).

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EP061

Hypertestosteronemia and primary infertility from a mediastinal extragonadal germ cell tumor

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A 26-year-old Caucasian male presented to the joint infertility outpatients clinic with primary infertility. His medical history included hypertrophic cardiomyopathy (HCM) due to genetically confirmed *MYH7* sarcomere protein mutation, treated with implantable cardioverter-defibrillator while his partner was a healthy 24-year-old Caucasian nulliparous female. Initial investigations showed hypertestosteronemia (Testosterone: >51.0 nmol/L) and azoospermia, hence the couple was referred for endocrine review. During consultation, he reported hoarseness of voice, hypersexuality, and increased hair distribution over the past 3 years. He denied ever having used anabolic steroids and was only on amiodarone to ameliorate arrhythmias from his known HCM.
On examination he was hirsute with bilaterally small testes (<10 ml). A testicular/scrotal ultrasonography was unremarkable. Subsequent investigations revealed elevated testosterone (52.9 nmol/L), b-hCG (900 IU/L) and suppressed FSH and LH: <1IU/L. The provisional diagnosis of an extragonadal germ cell tumor (EGCT) was made and whole body contrast enhanced CT revealed a $7\times 6\times 5$ cm mass of the anterior mediastinum without further disease dissemination. Due to his HCM and reduced ejection fraction (EF) : ~35% he was not eligible for neo-adjuvant treatment with bleomycin-etoposide-cisplatin (BEP), in view of the increased risk for cardiotoxicity. He was instead referred for transthoracic resection of the tumor, which he had uneventfully with R0 resection margins. Immediately following excision of the mediastinal mass, his testosterone dropped to undetectable levels (Testo: 1.0 noml/L) confirming that the mediastinal mass was the source of β-hCG driven testosterone hypersecretion. Histopathology revealed a mixed primarily seminomatous (95%) with minor teratomatous (5%) component EGCT. After surgery, considering his HCM, he was offered 1 high-dose adjuvant carboplatin cycle (6 AUC). He was not referred for surgical sperm extraction before chemotherapy because of the low risk of gonadal toxicity from carboplatin. At last follow-up, his testosterone was normal (18.7 nmol/L) without evidence of disease recurrence, and the couple was referred for microsurgical sperm retrieval followed by IVF with ICSI.

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EP062

Parathyroid adenoma, pituitary macroadenoma and raised gastrin levels in a patient with negative genetic testing for Multiple Endocrine Neoplasia Type 1: a mere coincidence?

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Background
Multiple Endocrine Neoplasia Type 1 (MEN1) is a rare autosomal dominant syndrome that predisposes individuals to multiple endocrine tumours, predominantly affecting the parathyroid, anterior pituitary and pancreatic islet cells. This unusual case shows features of three of the main MEN1 tumour types, yet genetic testing was negative for the MEN1 mutation.
Case esentation
A 56-year-old lady first presented with hypercalcaemia. She was fit and well and took no regular medications. There was no significant family history. She was investigated for a cause of her primary hyperparathyroidism [Ca^{2+} = 2.9 mmol/L (<2.65); PTH = 11.9 μmol/L (1.3–9.3)], which identified a left inferior parathyroid adenoma. Between follow-up appointments, a transient ischaemic attack was suspected. The CT-head found a pituitary mass. Subsequent MRI-head identified a $16\times 12\times 10$ mm pituitary mass without compression of

the optic chiasm. Pituitary function tests were within normal limits, confirming a non-functioning adenoma. MEN1 was suspected warranting further investigation. Fasting gut peptides revealed elevated gastrin levels [375 pmol/L (0–40)]. With features of the three primary MEN1 tumour sites now present, she was referred for genetic testing and MR-pancreas and Octreotide imaging to investigate for gastrinomas. During this time, she underwent left inferior parathyroidectomy. MR-Pancreas and Octreotide imaging failed to identify gastrinomas. Genetic testing did not reveal partial or whole MEN1 gene deletion.
Conclusion
This unusual case demonstrates significant diagnostic and management challenges. Despite phenotypically exhibiting MEN1 features, there is no genotypic correlation. Current management consists of regular surveillance for tumour progression.

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EP063

Synchronous endocrine malignancies (adrenocortical carcinoma and metastatic papillary thyroid cancer) – case report

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A 65 year old government officer presented to ophthalmologist with sudden visual loss in the right eye. Noted to have a retinal haemorrhage and significantly elevated blood pressure. GP was asked to investigate further.
For reasons unclear yet fortuitous, the initial imaging arranged was a CT CAP which demonstrated a large adrenal mass (9 cm well defined, heterodense, retroperitoneal right soft tissue mass of 40–70 HU with areas of necrosis) hence referral.
On review the patient gave a 6 month history of rapid weight gain, ankle swelling, thin skin with easy bruising and muscle weakness.
Physical examination was consistent with Cushing's syndrome and this was confirmed biochemically. Urine steroid profile showed increased cortisol metabolites in keeping with Cushing's but no steroid markers to suggest cancer.
Patient underwent right laparoscopic adrenalectomy; histology consistent with an adrenocortical carcinoma. Tumour had a mitotic count of 15 per 50 HPF indicating low grade. Patient was prescribed mitotane which she was unable to tolerate.
Post-op PET/CT reported a right cervical soft tissue mass. On US scan this was described as a 35×25 mm cyst in right side of neck at the level of thyroid cartilage; additionally a 10 mm U2 nodule in right lobe of thyroid gland was noted.
An US guided biopsy of the cystic mass was performed the histology suggestive of metastatic (adrenal) disease although features were not typical for adrenocortical carcinoma. Following excision of the neck mass, histopathology reported lymph node containing metastatic papillary thyroid carcinoma.
Patient proceeded to total thyroidectomy and neck dissection; histology reported a 9 mm classical papillary thyroid microcarcinoma with venous invasion. Radio-iodine therapy is scheduled.
A recent PET/CT has shown disease recurrence in the right surgical bed and additionally a peritoneal nodule in the right upper quadrant of the abdomen with further surgery planned.

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EP064

Case report of adrenocortical carcinoma in a nigerian woman

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Background
Adrenocortical carcinoma (AC) is relatively rare (0.02–0.2% of all cancer-related deaths), and can have protean clinical manifestations. Majority of cases are metastatic at the time of diagnosis, with the local periadrenal tissue, lymph nodes, lungs, liver, and bone as commonest sites of spread. Early detection of tumors is crucial for curative resection.
Case
A 63-year old Nigerian businesswoman was found to have a large right adrenal tumor while being investigated for chronic anemia. She is a known hypertensive for about 10 years controlled with Nifedipine. Younger sister died from adrenal cancer in the USA 2 years earlier.
She was admitted into the hospital because of complaints of profound tiredness, poor appetite and poor sleep and for investigation of the chronic anemia. Her hematocrit level had dropped from 31 to 22.3% within 2 months. There were no indications of chronic blood loss from the GIT or par vaginam and no renal disease.
Her examination showed in addition to palor, a large right hypochondrial/loin mass that abdominal ultrasound and CT scans showed was a large solid right suprarenal mass (13.8 cm×12.8×12.1 cm) with a few calcific foci (soft tissue density 30–40HU) and compressing the right kidney and liver. Post-contrast, there was mild heterogenous, predominantly peripheral enhancement with central non-enhancing area (40-70HU). Multiple abnormal vascular channels were seen within the mass. But no obvious invasion of visualized abdominal organs or surrounding right renal vein or IVC.
Her serum/plasma sodium, phosphate,calcium, aldosterone, rennin, TSH, cortisol, metanephrine and normetanephrine were within normal limits. But she had hypokalemia that was corrected with spironolactone and KCl (both oral and infusion) and low-normal magnesium.
At surgery, a well encapsulated adrenal solid mass, weighing 2000 g was removed and histology findings were those of adrenocortic al carcinoma.
She is being followed up by the oncologist, surgeons and physicians at the out-patient clinics.

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Neuroendocrinology and Pituitary

EP065

A rare case of primary suprasellar meningeal melanocytoma associated with nonfunctional pituitary adenoma

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Introduction
Pituitary adenomas are the most common pituitary tumours, but in 18% of cases we can find other rare tumours like: Rathke's cleft cyst, craniopharingyomas, chordomas, meningiomas, infiltrative or infectious disease. Meningeal melanocytoma is a benign neoplasm of central nervous system, commonly located in the base of the brain, cerebellopontine angle and the pineal body, difficult to differentiate from a nonfunctional pituitary adenoma before surgery.
Case report
We present the case of a 63-year-old man who presented 15 years ago for the evaluation of a nonfunctional pituitary adenoma. He developed sudden onset unilateral hemianopsia, and the MRI exam revealed a voluminous sellar and parasellar mass, protrusive in the sphenoid and cavernous sinuses. Partial transfrontal resection of the tumor was performed, and the pathology and immunohistochemistry diagnosed a 'null cell' nonfunctional pituitary macro-adenoma. Due to the presence of a progressing, large, residual mass, radiotherapy was recommended and performed and the patient developed global hypopituitar-ism. After radiotherapy the patient presented with initial tumor regression, but in the following 14 years the tumor progressed, with narrowing of the visual field, requiring a new neurosurgical, transsphenoidal resection. The pathology revealed meningeal melanocytoma, and the diagnosis was confirmed by immunohis-tochemistry: positive for melan A, S-100 and HMB45 and negative for CK19, CK20 and GFAP, with low-grade proliferation risk Ki-67 = 1–2%.
Conclusions
The association between meningeal melanocytoma and nonfunctional pituitary adenoma it is uncommon and represents a challenge for diagnostic and treatment. The gold standard therapy is complete surgical resection, but in cases with large residual tumoral mass or high proliferation risk, high-dose radiotherapy is recomended. Although benign, the meningeal melanocytoma can occasionaly relapse and present with malignant transition, so careful imaging surveillance is recommended.

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EP066

Case report: Indolent IgG4 hypophysitis with partial anterior pituitary failure

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A 79-year-old man presented with a fall and vomiting. The finding of significant postural hypotension associated with severe hypotonic hyponatraemia (Na 114 mmol/L, Osmolarity 244 mmol/L) mandated a Short Synacthen Test (cortisol 98 mmol/L at baseline and 238 mmol/L 30-minute post synacthen) and ACTH (6 ng/L) which confirmed central hypoadrenalism. This led to revelation of multiple pituitary axes involvement: hypogonadism (testosterone 1.1 nmol/L, FSH 1.3 U/L, LH 1.1U/L), growth hormone deficiency (IGF-1: 5 nmol/L), and partial central diabetes insipidus confirmed on a water deprivation test. The prolactin and thyroid test were normal. Confrontation visual field test was unremarkable. The MRI pituitary then revealed a normal pituitary gland with thickened stalk up to 5 mm. A discussion at pituitary multidisciplinary meeting (MDT) raised suspicion for lymphocytic hypophysitis and led to IgG4 level measurement, which was markedly elevated at 12.7 g/L (0-1.3 g/L). Granulomatous infiltration was less likely in this context especially with normal calcium and ACE level. A screening for systemic IgG4 disease with CT thorax and abdomen revealed multiple hilar and mediastinal lymphadenopathy, measuring up to 1.3 cm. These findings were stable on serial imaging which precluded bronchoscopy.

On this ground, a diagnosis of IgG4 related hypophysitis was entertained. In the absence of sight-threatening radiological findings or debilitating symptoms such as headache, high dose steroid was not required as the condition was deemed to be indolent. Patient's symptoms responded to physiological hydrocortisone and testosterone replacement and remained so for the subsequent 3 years of follow-up. Serial annual MRI pituitary consecutively showed non-progressive findings.

Discussion

While acute hypophysitis presenting with florid symptoms or ophthamological involvement may require high dose steroid, this case presented as indolent 'burn-out' disease was safely managed with mere hormonal replacement with no evident progression in the 3 year of follow-up. Histological confirmation may not be possible or even meaningful in these settings.

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EP067

A case of plurihormonal TSHoma presenting as meningitis

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This 22 year old lady presented with Haemophilus Influenza meningitis. Given an unusual organism, she had an MRI which revealed an incidental pituitary macroadenoma extending into the right cavernous sinus and breaching the anterioinferior wall of the pituitary fossa. Thyroid function showed raised T4 (24.7 pmol/L) and T3 (8.3 pmol/L) with unsuppressed TSH (1.75 munit/L). IGF-1 was also raised at 56.7 nmol/L (12–50.1 nmol/L).

Clinically, she was mildly thyrotoxic but not obviously acromegalic. Pending transphenoidal surgery, Lanreotide was started which normalised thyroid function and IGF-1 but she developed a CSF leak and a second episode of meningitis. After treatment and resolution of meningitis she had transsphenoidal adenomectomy and histology showed a plurihormonal atypical tumour with 30% expression for GH, 1% expression for TSH and Prolactin and MIB-1 index of 5–10%. Post op MRI showed residual tissue in the pituitary fossa and cavernous sinus.

After surgery, T3, T4 and TSH are in normal range at 5.1 pmol/L, 14.7 pmol/L and 1.68 munit/L respectively. However, IGF-1 level has started to rise above the normal range at 56.4 nmol/L She will be assessed in clinic following growth hormone day curve and indication for somatostatin analogues reviewed. This case is of interest diagnostically and in therapeutic challenges. Firstly it is relatively uncommon to have a plurihormonal pituitary adenoma presenting with meningitis and largely secreting TSH and GH with thyrotoxicity the most obvious clinical manifestation. Secondly, it is possible that initiation of somatostain analogue and subsequent tumour shrinkage may have precipitated the second CSF leak and subsequent meningitis. This young woman may need further therapy for residual tumour and it is uncertain if risks and cost of further treatment with somatostain analogue will outweigh benefit in this case.

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EP069

A mysterious pituitary adenoma

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A 33-year-old Caucasian female presented with ten-months history of amenorrhea and two months history of spontaneous galactorrhoea. She had a successful IVF pregnancy with embryo transfer 3 years previously for unexplained infertility. Her Body Mass Index was 37. No symptoms or signs suggestive of hypercortisolism or acromegaly. Her pituitary profile showed prolactin: 1698 IU/ml (40-500) and raised IGF1: 416 mcg/l (109–324), with normal Follicular Stimulating Hormone, Luteinizing hormone, Steroid Hormone Binding Globulin, estradiol, cortisol and Thyroid Function Test. OGTT with GH measurements were normal including IGF1 binding protein 3: 3.6 ug/l (1.7-5.2). MRI head revealed Pituitary macroadenoma15$\times$21$\times$19 mm. She was commenced on cabergoline 250 mcg/week.

After 6 months on treatment, she had regular periods with no galactorrhoea, but had new symptoms of fatigue and excessive sweating. Her weight remained stable. No symptoms or signs suggestive of hypercortisolism. No signs of acromegaly. Her prolactin was suppressed (36 IU/l) but IGF1 415 mcg/L level remained high. Repeat OGTT with GH measurement showed unsuppressed GH suggestive of acromegaly. She recovered from an episode of mild pituitary hemorrhage. She was commenced on levothryoxine therapy. Repeat MRI showed enlarging pituitary adenoma 18$\times$22$\times$23 mm. Referred for neurosurgical intervention.

Cabergoline was stopped and patient had transphenoidal resection that revealed aggressive Acidophilic stem cell pituitary adenoma with negative GH immunostain. Postoperative MRI pituitary showed no residual tumor. Hormonal profile showed raised prolactin 708 IU/l pending IGF1 level. Clinically she remains asymptomatic and awaiting treatment for uterine polyp and also planning embryo transfer IVF in near future.

Acidophilic stem cell pituitary adenoma is a rare aggressive tumor. It is an immature neoplasm developing from common progenitor cells of the growth hormone and prolactin cells. In our patient, clinical and biochemical evidence of acromegaly was revealed once on Cabergoline therapy, interestingly immunostaining was negative for GH.

Keywords: IVF- invitriofertilization, IGF1- insulin growth factor 1, OGTT- oral glucose tolerance test, GH- growth hormone, MRI- magnetic resonance imaging.

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EP070

Tolosa hunt syndrome: a rare cause of hypopituitarism

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Introduction

Tolosa Hunt Syndrome (THS) is a steroid-responsive idiopathic inflammatory condition affecting cavernous sinus and/or orbital apex causing painful ophthalmoplegia. We present a rare case of THS resulting in hypopituitarism.

Case

45-year-old female presented with 10-day history of headache, periorbital pain and diplopia. Past medical history included bipolar disorder and bilateral below knee amputation from rail accident. Drug history: mirtazepine, olanzapine and epilim. On examination, left abducens nerve palsy was noted with no other neurological/ophthalmological abnormalities. Haematology, biochemistry, autoimmune screen, angiotensin converting enzyme (ACE) were normal. MR angiography showed hyperintense lesion in left cavernous sinus suggesting inflammatory tissue, but no vascular or pituitary abnormalities were noted. A diagnosis of THS was made, and prednisolone 60 mg/day was commenced. Ophthalmic pain subsided within 48 hours; ophthalmoplegia resolved over 3 months leading to steroid cessation.

Progression

Six months later patient developed polyuria, polydipsia, tiredness and weight loss. Biochemistry revealed new onset type 2 diabetes mellitus and secondary hypothyroidism. Symptoms improved with levothyroxine and diabetes treatment, but full pituitary evaluation was not undertaken. Evaluation 10 years later by an Endocrinologist revealed partial anterior hypopituitarism: secondary hypothyroidism (TSH 1.4 miu/L {0.3–5}, FT4 6.9 pmol/L {9–25}), secondary hypogonadism (LH)

Discussion

THS is a rare cause of hypopituitarism with unknown aetiological mechanism. 5 of 7 cases reported with this association are of Japanese descent; 5 of 7 had

diabetes insipidus. 1 of 7 died of cerebral venous thrombosis; 6 recovered with high-dose steroids, and 2 patients showed full pituitary recovery.

Learning points

1. THS diagnosis should be suspected with presentation of painful ophthalmoplegia and full pituitary evaluation should be undertaken.
2. Symptoms usually resolve with high dose steroids but hypopituitarism is a recognised chronic complication.

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EP071

Cushing's disease caused by pituitary macroadenoma exhibiting Crooke's hyaline changes and immunoreactivity for adrenocorticotrophic hormone and growth hormone

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Introduction

Cushing's disease is usually caused by functional corticotroph microadenomas of the pituitary. Crooke's cell adenomas are rare, representing approximately 2% of corticotroph adenomas and mostly present as aggressive macroadenomas. Pituitary adenomas showing immunoreactivity for both ACTH and GH are also very uncommon. We present two cases of Cushing's disease caused by macroadenomas with Crooke's cell changes and immunoreactivity for ACTH and GH.

Case #1

A 51-year old woman presented with a self-limiting episode of right eye visual loss. MRI revealed a 21 × 19 mm pituitary macroadenoma. Arterial hypertension, long-standing irregular periods and 1-year history of tiredness were noted. Investigations confirmed ACTH-dependent hypercortisolism. CRH-stimulation test showed a flat ACTH response (max. rise from baseline below 20%) and cortisol rise from baseline of approximately 50%. The patient underwent endoscopic trans-sphenoidal surgery (ETSS) in June 2016 with a post-surgery cortisol 60 nmol/L. Immunohistochemistry showed moderate diffuse immunoreactivity for ACTH and GH. Extensive areas of Crooke's hyaline changes were detected in the adenoma tissue. The Ki67 labelling fraction was $<3\%$ with no evidence of P53 mutation.

Case #2

A 50-year old man presented with tiredness and erectile dysfunction and was found to have secondary hypogonadism and hypothyroidism. Arterial hypertension, obesity and obstructive sleep apnoea were noted. MRI detected a 27 × 19 × 23 mm macroadenoma. Investigations confirmed ACTH-dependent hypercortisolism. He underwent ETSS in April 2017 with good outcome (post-surgery cortisol 31 nmol/L). Histology revealed extensive Crooke's cell changes with strong immunoreactivity for ACTH and widespread GH staining. The Ki67 labelling fraction was low with no evidence of P53 mutation.

Neither patient had clinical or biochemical features of acromegaly.

Conclusion

To our knowledge cases of Cushing's disease caused by Crooke's cell adenomas with immunoreactivity for ACTH and GH have never been reported. These tumours should be considered as high-risk for recurrence warranting strict surveillance.

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EP072

Multi-drug resistant hyperprolactinaemia – a rarity or a rising entity?

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A 22-year-old female first presented in 2008 with a six-month history of galactorrhoea and irregular menses. She had hyperprolactinaemia (2401 mIU/L), a negative macroprolactin screen and her pituitary MRI scan demonstrated a 4 mm microadenoma. Her cannulated prolactin levels were > 1500 mIU/L. TFTs, IGF-1, cortisol and remaining pituitary profile were within normal range.

Cabergoline was commenced and gradually increased to 2 mg twice a week because of a poor response to therapy. Other than one serum prolactin of 486 mIU/L, her prolactin levels all remained > 1000 mIU/L. She always reported good concordance with medication. Resistance to drug therapy was confirmed by admitting the patient to hospital where she received medication under supervision and despite this, her serum prolactin did not decline. She was thereafter switched to Bromocriptine and titrated to a maximum dose with no biochemical or clinical response. Treatment with Quinagolide (up to 150 mcg od) was also tried. This was poorly tolerated (headaches and nausea) and again unsuccessful in lowering serum prolactin levels. Pergolide was discussed, but not tried. She has had two further MRI scans in 2010 and 2015 that did not demonstrate a pituitary microadenoma. The patient is currently taking no dopamine agonist therapy, her latest prolactin is 1656 mIU/L, she menstruates 4 times a year and continues to experience galactorrhoea. She would like to conceive and has been referred to a fertility specialist.

A subset of patients with hyperprolactinaemia, due to a prolactin secreting pituitary tumour, are resistant to dopamine agonist therapy. Resistance is believed to be mediated by loss of pituitary D2 receptors and this may occur in micro- and macroadenomas. A reduction in tumour size (as in our case), but failure to normalise serum prolactin levels has been described. Treatment options in such cases could include transsphenoidal surgery or radiotherapy. Our case further highlights these treatment challenges particularly in a young patient trying to conceive.

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EP073

Distracting spontaneous refractory hypoglycaemia

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Case

A 79 years old frail lady with history of dementia and hypertension presented with refractory hypoglycaemia over a period of 3 months requiring multiple admissions. During her most recent admission, she required continuous dextrose infusion to maintain euglycaemia. The severe spontaneous hypoglycaemia in this non-diabetic lady, warranted a series of investigations. TFT and Short Synacthen Test excluded thyroid dysfunction and hypoadrenalism. The anterior pituitary profile including prolactin, LH, and FSH were all normal. Two separate samples of IGF-I was 8 nmol/L and 6.6 nmol/L (10–25 nmol/L). CT scan with contrast of the abdomen and pelvis revealed a heterogeneously enhancing mass (6.6 cm) arising from the lower pole of the left kidney consistent with renal cell carcinoma. Concomitantly there were extensive peripherally enhancing heterogeneous mass lesions in the liver, the largest measuring at 12 cm. The pancreas was normal. IGF-II:IGF-I ratio during the event of hypoglycaemia (blood glucose 1.6 mmol/L) was less than 10, which was inconsistent with non-islet cell tumour induced hypoglycaemia (NICTH). Inappropriate elevation of C-peptide 4210 pmol/L (174–960 pmol/L) and Proinsulin > 200 (0–7 pmol/L) was noted, along with a suppressed Insulin at 12 pmol/L (0–180).

In view of multiple comorbidities, a palliative approach was taken. The post-mortem confirmed a clear cell renal carcinoma of the left kidney. Unexpectedly, the morphology and immunoprofile of the liver metastases were consistent with proinsulin secreting neuroendocrine tumour. The immunostaining showed focal strong insulin immunoreactivity, as well as widespread CD56, synaptophysin, and chromogranin A, with negative staining for RCC.

Discussion

Proinsulinoma is a rare condition and can be masked by concomitant metastatic malignancy. Multiple hepatic metastases is a well-known cause of spontaneous hypoglycaemia. However, in severe intractable hypoglycaemia, coexistence of insulin secreting tumour needs to be considered to avoid missing them.

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EP074

Recurrent lymphocytic hypophysitis during two pregnancies: a very rare case

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Lymphocytic hypophysitis (LyH) is a rare condition often associated with pregnancy (usually presenting in the last month of pregnancy or in the first two post-partum months). We describe a very rare case of recurrent LyH during two pregnancies.
A 25-years old woman presented in 7/2003 with a 6-week history of headaches and a 2-week history of visual deterioration whilst 38 weeks pregnant. Bitemporal hemianopia was confirmed and pituitary MRI revealed a sellar mass deforming the chiasm. Secondary hypothyroidism was found and levothyroxine was started. Hydrocortisone was also added. She had induction of labour two days later and she delivered a healthy boy. Two days after delivery, she had urgent transsphenoidal removal of the mass; pathology was consistent with LyH. Post-operatively, she made good recovery with marked visual improvement. Short Synacthen test was normal and she was breastfeeding. Pituitary MRI (11/2003) revealed a small amount of tissue within an enlarged fossa with no significant suprasellar extension. In 1/2004, she conceived again and at the 14th week of pregnancy she was experiencing increasingly generalised headaches and bilateral visual disturbance. MRI (3/2004) showed pituitary enlargement elevating the chiasm. She had bitemporal field defects and she was put on hydrocortisone (final dose: 30 mg am, 15 mg pm). In the subsequent weeks, she had close visual monitoring and no further deterioration was detected. In 9/2004, she delivered a healthy boy. Post-partum, her vision returned to normal and follow-up imaging showed gradual resolution of the LyH. Her periods returned and adequate ACTH reserve was confirmed. She had no further pregnancies. In her latest follow-up (12/2016), she is on levothyroxine and GH replacement.
Although, it has been suggested that a history of LyH in pregnancy does not increase the risk of developing LyH in subsequent ones, our case demonstrates the variable natural history of this condition.

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EP075

A rare case of *SDHB* mutation in a male individual with pituitary adenoma, and paraganglioma/phaeochromocytoma syndrome

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Introduction
Herein we provide clinical, biochemical, histological and radiological evidence of a rare case of a male patient who was diagnosed with pituitary macroadenoma (prolactinoma), phaeochromocytoma and a lung typical-carcinoid tumour on a background of *SDH* gene mutation encoding the succinate dehydrogenase enzyme.
Presentation of case
A 42 year old male individual, was initially diagnosed with a pituitary macroadenoma (prolactinoma) after complaining of persisting severe headaches, for which cabergoline treatment had been initiated.
His positive paternal history of phaeochromocytoma, led to further genetic screening which revealed a c.600>A, p.(Trp200*) mutation in the *SDHB* gene and further biochemical and imaging studies confirmed the presence of a phaeochromocytoma, which was surgically excised.
Following a random hospital visit, a plain chest radiograph raised concerns over a right lower lobe mass which ultimately led to advanced imaging studies with CT and PET, confirming the presence of a neoplastic lesion with no evidence of lymphadenopathy of other evidence of metastatic disease.
A subsequent lobectomy and Histopathological analysis (positive for chromogranin and synaptophysin) confirmed the diagnosis of a typical carcinoid tumour (stage pT1b N0 Mx).
Discussion
The role of mutations in the genes encoding the succinate dehydrogenase (SDH) subunits, in tumorigenesis has been described previously and especially the predisposition to the development of the hereditary paraganglioma/phaeochromocytoma syndrome (HPGL/PCC).
To our knowledge this may be the first reported case of a lung neuroendocrine tumour, phaeochromocytoma and pituitary macroadenoma on the background of a mutation in the *SDHB* gene.

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EP076

Secretory Head and Neck Paraganglioma – A rare entity

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We report a case of 43 year old gentleman who had surgery in 1998 for left glomus typanicum, leaving him with complete left lower facial nerve palsy. Incidentally he was noted to have had labile blood pressure during this surgery. He had gradual growth of residual tumour which required fractionated radiotherapy in 2012. He has had ongoing problems with headaches with profuse left-sided rhinorrhoea and intermittent episodes of sweating. In February 2016 he was referred to ENT for evaluation of his symptoms. His urinary catecholamines showed methoxytyramine 5.17 umol/24 hr (reference range succinate dehydrogenase B (*SDHB*). A likely indolent left level IIb nodal metastasis was identified on FDG PET scan. The iodine-123-meta-iodobenzylguanidine (M IBG) scan demonstrated no increase uptake in the lesion. However, a skull base mass lesion and lymph nodes were avid on 68-Ga- DOTATATE PET CT. This is in keeping with recent finding that lesions due to *SDHB* mutations are more likely to be avid on 68-Ga-DOTATATE scans. The patient was symptomatic and the biochemical markers confirmed the lesion to were functional (no other lesions were identified on scans). The utility of the Ga-68 DOTATE PET scan has provided a treatment option Lutetium based Peptide Receptor Radionuclide Therapy (PRRT).
This case highlights that, though rare, head and neck paragangliomas can be secretory. Furthermore, the utilisation of appropriate functional imaging can be quite important in the treatment pathway. Genetic testing was carried out relatively late during the course of the management of this patient which may have given important information about likely course of the disease as well as imaging modalities that may have been useful in the detection of the disease.

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EP077

AIP mutation causing familial pituitary tumours

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Familial isolated pituitary adenoma (FIPA) is an increasingly recognised cause of familial pituitary tumours with autosomal dominant inheritance. An increased population risk of AIP mutations has recently been reported in Ireland. We present the cases of three siblings, with likely AIP related disease, attending endocrinology clinics in Glasgow. Patient one has been confirmed to be an AIP mutation carrier.
Patient 1 was referred in 2006, aged 46. She has a history of anxiety, and presented with galactorrhoea and secondary amenorrhoea. Prolactin was 4400 mIU/l and remained elevated after withdrawal of risperidone. Pituitary function was otherwise normal. MRI showed a 9 mm microadenoma, and treatment with cabergoline was initiated. Her compliance with treatment has been intermittent, and claustrophobia has made further imaging intolerable.
Patient 2 also has a history of anxiety. She was referred in 2008, aged 44, with secondary amenorrhoea and prolactin 3000 mIU/l. Remaining pituitary function was normal. She was unable to tolerate MRI, but CT has shown an 8 mm lesion. Imaging and prolactin levels have remained static despite treatment with cabergoline 2 g/week.
Patient 3 was referred in 2012, aged 47, from his optician with bitemporal hemianopia. Initial bloods demonstrated panhypopituitarism with prolactin of 199,490 mIU/l. MRI revealed a giant macroadenoma with suprasellar extension and secondary hydrocephalus. He was transferred to neurosurgery, but was managed medically. He remains on cabergoline 2 g weekly and full pituitary hormone replacement, imaging has shown a substantial reduction in tumour bulk. Patient 1 has tested positive for the AIP mutation. The family have since been referred to genetics for screening and counselling. These cases demonstrate the importance of obtaining an accurate family history. Current data support the testing of AIP mutations in patients presenting with pituitary tumours at a young age, or with a family history of pituitary disease.

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EP078

A partial hypopituitarism case that resolved following bariatric surgery

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Background
The use of opioids in non-cancer patients has increased dramatically over the past few years. The most common endocrine dysfunction with opioid use is hypogonadism, but it has been reported in a small number of cases that adrenal insufficiency and adult growth hormone deficiency can also occur.
Clinical case
A 39 year old male presented with general fatigue, loss of libido and sweating for about six months in 2008. He suffered from severe back pain, neck pain and was on morphine sulphate tablet 30 mg BD. The past medical history included T2DM and obesity. In clinic he was overweight (BMI 42) with sparse body hair. His blood tests showed testosterone 5.7 nmol/L, FSH 1.9 U/L, LH 0.8 U/L, Prolactin 514, TSH 2.9 mU/L, FT4 12 pmol/L and 9 am Cortisol 63 nmol/L. MRI pituitary was normal. His partial hypopituitarism was likely due to chronic opioid use. He was commenced on hydrocortisone and testosterone, followed by growth hormone replacement after having dynamic pituitary function tests. In December 2015 he underwent bariatric surgery and lost 36 kg weight in total. In 2016 his BMI was 33.6; he was no longer on morphine tablets or any treatment for diabetes (HbA1c 42 mmol/mol). In 2017, repeat dynamic tests showed his peak GH and cortisol levels were satisfactory. At present, he remains only on testosterone replacement.
Conclusion
This is one of very few cases demonstrating the effect of opioids on GH levels, other than causing hypogonadism. More research is needed to determine which opioids are more likely to cause endocrine dysfunction and which patients need to be screened and treated.

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EP079

Siadh associated with neuromyelitis optica involving hypothalamus

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A 21 year old Asian woman presented with relapse of Neuromyelitis Optica (NMO) spectrum disorder, diagnosed aged 16. She had headache, dizziness, right hand weakness and severe hyponatraemia (serum sodium [Na^+] 116 [135–145]). Emesis, dominant in previous relapses, was absent – she was euvolaemic. Serum (Seosm) and urine (Uosm) osmolalities were 250 and 468 mosm/kg respectively, thyroid function normal. Medications included Prednisolone 20 mg daily, Azathioprine, and proton-pump-inhibitor converted to histamine2-receptor-antagonist. Hyponatraemia improved to 129 with fluid restriction, diagnosis being syndrome of inappropriate antidiuretic hormone (SIADH) secretion.
2-weeks later she reported increasing somnolence, increased frequency of urination without evidence of infection, and unchanged thirst. Documented fluid balance over a 24-hour period was normal as were repeat paired serum and urine test results (Na^+141, Se_{osm}293, U_{osm}698). She appeared emotionally labile, expressed suicidal ideation, and fell into deep sleep mid-consultation precipitating urgent admission for treatment of further relapse. Somnolence was likely secondary to central sleep apnoea confirming neurological progression as sodium was normal. MRI brain showed florid inflammatory change in the region of the hypothalamus.
NMO is an autoimmune disease, predominantly affecting optic nerves and spinal cord but also certain brain regions, is associated with the presence of IgG antibodies to aquaporin-4 (highly expressed in hypothalamus, brainstem, periventricle & spine). Minority proportion (case-series, case-reports) is associated with endocrinopathies involving hypothalamus-pituitary (hyperphagia and obesity, hyperprolactinaemia, amenorrhoea-galactorrhoea); and diabetes mellitus, hypothyroidism & hypoparathyroidism. Hyponatraemia due to SIADH, may occur only at the beginning of a relapse, or persist through it and later resolve. Diabetes Insipidus (central or nephrogenic-unclear) has been reportedly associated less commonly than SIADH.

KEY-POINTS
1. Unlike autoimmune idiopathic hypophysitis which typically causes central-DI, SIADH has been reported more commonly with NMO.
2. SIADH may reportedly precede an exacerbation of NMO, or accompany & resolve after a relapse.
3. Increasing awareness of NMO-associated-endocrinopathy needed.

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EP080

Paraneoplastic Cushing's syndrome associated with neuroendocrine tumour of the pancreas: A case report and review of literature

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Paraneoplastic Cushing's syndrome is a rare disease and is usually associated with small lung cancer or bronchial carcinoid tumour. In this case report we present an unusual case of metastatic neuroendocrine tumour of the pancreas presenting with florid Cushing's syndrome.
A 45-year-old female presented with four-month history of worsening blurred vision, dry mouth and lethargy. In the hindsight, for the past three years she had weight gain, easy bruising, oligomenorrhoea, facial flushing and difficulty with activities such as walking upstairs and above head arm activities. She was hypertensive and hypokalaemic in addition to the physical signs of facial plethora, interscapular fat pad, purple striae, central obesity, thin skin, leg bruises and proximal myopathy. Past medical history included Poland syndrome, PCOS and migraines.
A clinical diagnosis of Cushing's syndrome was made and 9am cortisol and ACTH level identified to be significantly raised, re-confirmed with 48-hour low dose dexamethasone suppression test. MRI head did not identify a pituitary tumour. CT abdomen showed a tumour in the pancreatic tail with multiple metastatic lesions in the liver. Liver biopsy confirmed well differentiated neuroendocrine carcinoma. Patient was medically managed with metyrapone and spironolactone with some symptomatic improvement, and she was referred to tertiary neuroendocrine centre for further management.

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EP081

A rare case of a functioning retroperitoneal paraganglioma in a patient with recurrent Phaeochromocytoma/Paraganglioma (PPGL)

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Paragangliomas are rare neuroendrocrine tumours arising from extra-adrenal paraganglia of the autonomic nervous system and excess catecholamine secretion is associated with higher cardiovascular morbidity and mortality. We present the case of a 56-year old male referred to our outpatient clinic with symptoms of sympathetic-hyperactivity, including excessive sweating, palpitations and diastolic hypertension (140/100 mmHg). He had undergone bilateral thoracotomy and laparotomy on separate occasions in Poland many years ago to remove paragangliomas in the head, neck and abdomen. He also reported a strong family history of paraganglioma/phaeochromocytoma type 1 (PPGL-1) in his father, paternal grandfather, brother, sister and aunt. Polish medical reports document a mutation in the SDHD gene consistent with high genetic penetrance, however there had been a loss to follow up from routine surveillance. Current medications included doxazosin 4 mg daily. 24-hour urinary catecholamines revealed: Normetadrenaline 14304 nmol/24 hr (0–3300 nmol/24 hr), Metadrenaline 132 nmol/24 hr (0–1200 nmol/24 hr), 3-Methoxytyramine 979 nmol/24 hr (0–2500 nmol/24 hr). CT-imaging showed a well defined retroperitonal aortocaval mass 4.4 cm × 4.5 cm at the level of L2, displacing the aorta and IVC laterally. A left partially obstructing ureteric calculus was also seen. Due to significant biochemical activity of the suspected retroperitoneal PPGL, he was commenced on alpha-blockade with Phenoxybenzamine 10 mg 3x/day prior to propranolol 40 mg twice daily. Further imaging is presented including MRI head/neck and ^{123}I-MIBG scintigraphy and the patient was referred to the local Endocrine MDT in view of complete surgical resection and histopathological analysis. Genetic testing is also presented for MEN and SDH subtypes. This case highlights the importance of biochemical evaluation as part of routine follow-up in patients with known PPGL to detect recurrent disease, for example retroperitoneal

paragangliomas. It also highlights the importance of follow up of previously treated PPGL in the context of genetic syndromes for example SDH subunit mutations, which may result in a higher level of recurrent or metastatic disease.

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EP082

Ipilimumab induced hypophsitis. A new cause for a rare disease

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Ipilimumab is a monoclonal antibody that had been shown significantly to improve survival in cases of metastatic melanoma. It blocks cytotoxic T-lymphocyte antigen 4(CTLA4) resulting in T-cell activation, proliferation and antitumor response. However recently an emerging clinical entities of different endocrinopathies have been reported in patients on ipilimumab. These are mainly related to lymphocytic hypophysistis causing anterior hypopituitarism. We report a case of a 67 years old male who has metastatic malignant melanoma for which he was on ipilimumab therapy. His past medical history included dilated cardiomyopathy and atrial fibrillation. One week after his third dose of ipilimumab he developed postural dizziness, fatigue, nausea and headache. On admission to hospital he was lethargic and his blood pressure was 100/60. Investigations showed: serum sodium: 115 mmol/l. Serum potassium: 4.1 mmol/L. creatinine 114 mmol/L, Blood urea: 4.4 mmol/L. Pitutary profile was as follows: Serum cortisol at 6.30 am: 70 nmol/L. ACTH:11 ng/L(Normal range: 0–46 ng/L). TSH: 0.03 mU/L. FreeT4: 6.6 pmol/L. Testosterone $<$0.1 nmol/L. FSH: 1.3 IU/L. LH: 0.1 IU/L Prolcatin 450 mU/L, negative for macroprolactinemia. Before starting ipilimumab he had normal thyroid function and normal electrolytes. As these results confirmed panhypopitutarism he was started on oral hydrocortisone replacement therapy followed by thyroxin replacement and later testosterone replacement. His symptoms of lethargy and dizziness improved and his serum sodium normalized. Pituitary MRI showed showed diffuse enlargement of the pituitary gland, findings in keeping with the diagnosis of hypophysitis.

This case sheds the light on an emerging endocrine complication of one of the novel immunomodulation therapy. It highlights of the importance of of having a high index of suspicion of hypopituitarism in patients receiving ipiluimab therapyas the symptoms of hypopitutarism could be misinterprated as being caused by malignancy or side effect of chemotherapy. Screening for pituitary hormonal abnormalities is recommended especially after the third dose as the majority of cases of ipilimummab-induced hypophysitis occurred after the third dose.

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EP083

Secondary adrenocortical insufficiency and renal impairment in a patient presenting with Hyperprolactinaemia

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We report a rare case of 19 year old lady who was referred to us with galactorrhoea associated with hyperprolactinemia (PRL-1049 mU/L). MRI, arranged by GP, had revealed an enlarged pituitary with a 14$\times$8 mm macroadenoma slightly distorting the optic chiasma. Visual fields were normal on confrontation but showed restricted fields in both eyes on Goldman perimetry. She was commenced on cabergoline to which her galactorrhoea responded quickly. Full pituitary profile was not completed at the first visit, but she acknowledged some fatigue and slight cold sensitivity on direct questioning at a subsequent visit.

Her profile revealed severe primary hypothyroidism (TSH- 742 mU/L and fT4$<$ 3.4). Cortisol was 283 nmol/L; gonadotrophins were normal, as was her IGF-1. Her creatinine was raised to 141 umol/L, despite her slender built. Creatine Kinase was moderately elevated (297 iU/L). She was commenced on Levothyroxine 50 ug OD along with hydrocortisone (15 mg Am and 10 mg mid-afternoon). A short synacthen test, carried out less than 2 weeks after starting hydrocortisone, showed an abnormal response with cortisol rising from 108 to 289 at 30 minutes and 390 at 60 minutes. Her subsequent ACTH (after omitting hydrocortisone the previous evening and delaying the morning does till after the test) was 17.1 ng/L; cortisol was 30 nmol/L at the time. Adrenal antibodies were negative. In due course her visual fields improved on perimetry with slight regression in size of pituitary gland.

Her primary Hypothyroidism appears to have caused compensatory pituitary hyperplasia with associated hyperprolactinaemia due to high TRH +/− pituitary stalk compression and her pituitary hyperplasia also caused secondary adrenal insufficiency. Her hypothyroidism was sufficiently profound to cause renal impairment.

Learning points

The various aetiologies need to be borne in mind when assessing patients with hyperprolactinaemia. Primary Hypothyroidism should be considered as a potential cause. Modest prolactin rises should not be attributed to macroadenoma without other causes having been ruled out.

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EP084

Aggresive Ectopic ACTH production causing Cushing's

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Ectopic Cushing's syndrome is rare, accounting for 5–10% of all cases of Cushing's. The majority are casued by small cell lung cancer and neuroendocrine tumours.

We report a case of a 59 year old male who presented with osmotic symptoms after newly diagnosed diabetes, hypokalaemia and metabolic alkalosis with clinical features suggestive of Cushing's. Initial random cortisol was $>$2000 nmol/l and 24 hour urine cortisol 14500 nmol/l (99–378 nmol). Both low and high dose dexamethasone suppression tests failed to supress, being 2069 nmol/l and 2550 nmol/l respectively. ACTH was 580 ng/l ($<$50 ng/l). His pituitary MRI was normal. Adrenal CT showed bilateral adrenal hyperplasia suggestive of ectopic ACTH production with also evidence of liver metastases. A staging CT revealed a left hilar mass (T2bN3M1b). A liver biopsy confirmed poorly differentiated neuroendocrine tumour. Initial management included insulin and metyrapone. The cortisol levels decreased to 600–800 nmol/l. Diabetes control remained poor. Palliative chemotherapy with Carboplatin and Etoposide resulted in a marginal decrease in the size of the lung mass and liver metastases. Poorly controlled diabetes, recurrent infections, progressive oedema and proximal myopathy increased comorbidity. Follow-up scan 2 months later showed increasing size of the lung primary with additional metastases in the adrenals and bones with multiple pulmonary emboli. Second line chemotherapy provided some symptom relief however he deteriorated rapidly and died.

Ectopic ACTH production is associated with poor response to chemotherapy, short survival and a high rate of complications to therapy. Studies have shown variations in clinical course can be ascribed to aggresive transformation resulting in liver and adrenal metastases.

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EP085

Severe hypoglycaemia in a woman with secondary hypoadrenalism and an abnormal pituitary stalk, complicating metastatic breast carcinoma

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Introduction

Significant hypoglycaemia is a rare but well recognised presenting feature of secondary adrenal insufficiency. Such hypoadrenalism may be caused by intrinsic hypothalamo-pituitary disease (pituitary adenoma), exogenous steroid therapy, and uncommonly by hypophysitis and pituitary secondaries from malignant disease.

Case presentation

A 73-year-old woman presented acutely with confusion, agitation, and aggressive behaviour. She had been unwell for many months and had lost 3 kg in weight. She had ulcerative colitis, controlled with mesalazine but was on no other medication. She did not smoke and drank alcohol rarely. On examination she was thin and pale, had a pulse of 70/minute, BP 137/78, Temp 33.3 deg celsius. Systems examination was entirely normal. Paired capillary (0.3 mmol/l) and venous plasma (2.2 mmol/l) glucose were low. She was given intravenous dextrose.

Investigations - Na 131 mmol; short Synacthen test - cortisol 56 (0 min) and 297 nmol/l (30 min); adrenal antibodies −ve; plasma oestradiol 37 pmol/l, LH 0.1 mIU/ml, FSH 2.4 mIU/ml; prolactin 734 mU/L; TSH 0.81 mU/L, free T4 9.1 pmol; IGF-2/IGF-1 ratio 5 (normal $<$10). Insulin antibodies 2.8 (0.0–5.0), Gut hormone profile normal; Ca15-3 - 5581 ku/l ($<$32)

MRI pituitary showed a hypodense macroadenoma with a thickened stalk, and hypodense areas on the frontal bones with postcontrast enhancement. CT scans

showed lucent lesions in L2 and right sacrum, but normal adrenals. Isotope bone scans confirmed secondaries in the axial and appendicular skeleton with no obvious primary. Bone biopsy confirmed secondaries from an adenocarcinoma of the breast although ultrasound breasts and mammography were normal.

Discussion

Severe hypoglycaemia is an unusual presenting feature of secondary hypo-adrenalism, which needs to be considered in the differential diagnosis. This patient had partial anterior hypopituitarism likely due to pituitary metastases from a hitherto undiagnosed breast carcinoma. Although hypophysitis and pituitary adenoma are also possible, the finding of multiple bony secondaries and pituitary imaging characteristics make secondaries likely.

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EP086

Cushing's disease - Case report

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Introduction

Cushing's syndrome is caused by an extended exposure to increased levels of endogenous or exogenous glucocorticoids. It is a syndrome that can be extremely challenging to diagnose as many symptoms and signs are also indications of other disease processes.

Case

A 76 year old man presented to hospital with a six month history of immobility and falls. Proximal muscle weakness was also noted. The patient then underwent a period of rehabilitation.

The patient had a history of type 2 diabetes mellitus, hypertension, congestive cardiac failure, combined B12 and folate deficiency, longterm suprapubic catheter due to urinary retention, urinary tract infections and a myocardial infarction.

A first set of investigations revealed a 24 hr urinary free cortisol of 206 nmol/24 hr (0–146/24 hr), an overnight dexamethasone suppression test of 1588 nmol/L and a low dose dexamethasone suppression test of 1131 nmol/L ($<$50 nmol/L). The ACTH level was revealed to be 139 pmol/L and an MRI scan revealed a left-sided pituitary adenoma. As such, a diagnosis of ACTH-dependent Cushing's disease was made.

The patient was initially managed with metyrapone with a view to transphenoidal surgery. However the patient developed shortness of breath and worsening peripheral oedema. A chest X ray and echocardiogram revealed left ventricular failure and reduced systolic function, respectively. For this reason it was decided to medically optimize his congestive cardiac failure and hypercortisolaemia as an inpatient with progression to neurosurgery if he were to stabilize.

Discussion

Cushing's disease is a rarity that can be difficult to diagnose due to the significant number of varied pathologies indicated by its signs and symptoms. This is an interesting case of Cushing's disease as the levels of cortisol measured in the patient were incredibly high.

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EP087

A 32 Year old Nigeria Male with Azoospermia Who Presented with Bilateral Gynecomastia at The State Specialist Hospital Akure – A Case Report and Review of Literature

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Background

A case report of Nigeria male who presented on account of bilateral gynaecomastia and was found to be azoospermic on investigation with a view to draw attention of clinicians to underling endocrine problems associated with gynaecomasia.

Methodology

A case report of a 32 year old Nigeria man with progressive-bilateral breast enlargement was reviewed.

Case report

A 32 year old Nigeria male with bilateral breast enlargement since 2013 presented to the endocrine clinic on account of the progressive increase in size of the breast which was protruding from his cloth. There was positive history of occasional pain from the breast. No history suggestive of kidney, thyroid nor liver diseases. No history of use of recreational drugs nor any other drugs. Does not smoke but occasionally takes alcohol. No history of erectile dysfunction orprevious surgery to the pelvic region. Had similar problem at age of 18 years for which he was given some drugs by a nurse.

On examination, the breasts were enlarged 3.5 cm bilaterally and there were testicular atrophy (5 ml with orchidometer). Other physical examinations were normal.

Investigations showed elevated LH, FSH and prolactin with normal testosterone, estradiol, bHCG, liver function test and electrolyte and creatinine. Testicular ultrasound shows bilateral testicular atrophy with varicocele and semen analysis was azoospermic. MRI shows pituitary micoadenoma.

Patient was commenced on carbegoline and refers to the urologist for surgery. He was to continue with drugs and come back for hormonal assays and seminal analysis.

Conclusion

Early referral of patients with gynaaemosia to endocrine clinic is necessary for adequate clinical and biochemical assessment to determine the cause and prompt treatment to prevent irreversible complications.

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EP088

Was it Growth hormone deficiency?

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The short stature can be feature of uncontrolled diabetes due to low portal insulin levels causing decrement of IGF-1 and IGFBP-3 concentrations.

We describe the case of a 14 yrs old boy with Type 1 diabetes, who was admitted at our hospital in April, 2017 for the evaluation of short stature. He was the youngest of the nine older, normal statured siblings and was the shortest amongst his class-mates. He had not started shaving, his voice was not cracking and had no morning erections.

The patient was diagnosed with Type 1 diabetes, 2 years back. He never had ketoacidosis, but his blood glucose had been largely uncontrolled. He was non-compliant to insulin and diabetic diet. Systemic review was unyielding.

He was born through Caesarian section. The perinatal, developmental and nutritional histories were unremarkable. The patient was a student of Grade 9 with reasonable academic performance.

Type 1 diabetes and obesity were present amongst four and five of his family members, respectively. An elder brother had undergone sleeve gastrectomy.

He was on Glargine insulin, 35 units PM, Insulin Aspart 20 units AM & noon and 15 units PM and Glucagon, 1 mg, PRN.

On examination, the patient was fully conscious, comfortable & co-operative. He was vitally stable. BMI 29 kg/m^2 (Height 145 cms, mid-parental height 173.5 cms). His height and weight were $<5^{th}$ percentile and 75^{th} percentile for age, respectively General exam showed acanthosis nigricans at the nape of the neck only. Thyroid not enlarged. Tanner score 1 with pre-pubertal features. Rest of the general and systemic examination was unremarkable.

The complete blood count, liver & renal functions, bone & thyroid profile were unremarkable. HbA1c 10.3%, Total Cholesterol 5.63 mmol/L, LDL 3.59 mmol/L,TG 1.95 mmol/L, HDL 1.15 mmol/L, Total Testosterone 0.09 nmol/l, LH 0.4 IU/L, FSH 1.0 IU/L, S. Cortisol (AM) 133.7 nmol/l. Celiac antibodies absent.

Growth hormone stimulation with insulin, clonidine and exercise indicated blunted GH responses (6.74, 5.14, 2.84 ng/ml,respectively). IGF-1, 95 ng/ml (115-498).

His Bone age was according to the chronological age. CT scan pituitary was normal.

The patient was started on 4IU, S/C, Growth hormone on alternate days and referred to the intensive insulin therapy clinic.

Growth hormone and IGF-1 secretion can be influenced by obesity, uncontrolled diabetes, nutritional status, puberty, as in our patient.

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Obesity and Metabolism

EP090

Successful use of canagliflozin for treatment of post-bariatric surgery hypoglycaemia unresponsive to other therapy

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Reactive hypoglycaemia after gastric bypass surgery is characterized primarily by excessive postprandial hyperinsulinaemia and resultant neuroglycopaenic symptoms. The elusive pathophysiology of this problem has made treatment challenging. We describe the first case report where treatment with the Sodium Glucose Transporter Inhibitor canagliflozin has reduced hypoglycaemic episodes after failure of other therapies.

A 56 year old female with a history of obesity and diet controlled Type 2 Diabetes Mellitus underwent Roux-en-Y gastric bypass in 2011, resulting in weight loss of over 20 kilograms. Three years later she began experiencing almost daily episodes of symptomatic hypoglycaemia. Plasma glucose fell to 2.1 mmol/l postprandially without suppression of insulin (39.8 mU/L) or C peptide (6.25 nmol/L). Flash glucose monitoring with the Free Style Libre device confirmed postprandial spikes of hyperglycaemia with subsequent hypoglycaemia. MR imaging of the pancreas was normal, and anti-insulin antibodies and sulfonylurea screen were negative. Renal and liver disease and hypoadrenalism were excluded.

Dietary adjustments were advised and metformin commenced, with minimal improvement. Acarbose and octreotide were poorly tolerated due to gastrointestinal side effects.

A trial of canagliflozin 100 mg daily was offered to the patient before contemplating surgical reversal. She experienced immediate remarkable symptomatic improvement associated with reduction of both hyperglycaemia and hypoglycaemia, documented on both capillary and flash glucose monitoring. This was sustained over a 9 month follow up period, and was further confirmed by 1 week off and one week on canagliflozin.

Postprandial hypoglycemia has been successfully treated with an SGLT2 inhibitor in this gastric bypass patient after failed response to diet, metformin, acarbose and octreotide. Canagliflozin has helped to both reduce the frequency of hypoglycaemia and the degree of blood glucose excursion after carbohydrate. This case also demonstrates the usefulness of flash glucose monitoring in revealing blood glucose trends and response to treatment in such patients.

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EP091

The importance of the lows, and not the just the highs, of glycaemia in critical illness

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Stress hyperglycaemia is a widely recognised feature of critical illness. Spontaneous hypoglycaemia, by contrast, is an underappreciated but serious complication. Here I present three cases encountered over 12 months in a single teaching hospital.

Case 1: 59 year old female. Admitted with fever and leg pain. Cellulitis diagnosed and antibiotics commenced. Hours later, she became unresponsive and shocked, with evident necrotising fasciitis. She had metabolic acidosis, lactate 10.0 mmol/L. Capillary blood glucose was 0.8 mmol/L and serum cortisol was only 169 nmol/. Unfortunately, she deteriorated further and died shortly afterward. A post-mortem revealed bilateral adrenal haemorrhage.

Case 2: 43 year old male. Presented with respiratory distress following a viral prodrome. Blood gas analysis showed metabolic acidosis, lactate 7.0 mmol/L. Laboratory tests showed leukopaenia, coagulopathy, acute kidney injury and hepatic failure. He became diaphoretic and aggressive, followed by PEA arrest. Capillary blood glucose was 0.8 mmol/L. Unfortunately, he died on ITU 8 days later from multiorgan failure.

Case 3: 49 year old female. Admitted with abdominal pain, fever, diarrhoea and vomiting. She developed disorientation and confusion with capillary blood glucose 1.8 mmol/L. Tests revealed coagulopathy, acute kidney injury and hepatic failure. Cortisol was appropriate at 1261 nmol/L. After antibiotics and glucocorticoids in intensive care, she made a full recovery and remains under investigation for an as yet undiagnosed systemic inflammatory condition.

Spontaneous hypoglycaemia in critical illness is associated with high mortality – in one study of 7820 patients with acute MI, 136 (1.7%) experienced spontaneous hypoglycaemia (mean glucose 2.5 mmol/L), which was associated with a doubling of mortality. Increased metabolic demand requires effective mobilisation of energy stores to maintain blood glucose concentrations. Hypoglycaemia is most often found in the context of hepatic failure (disruption of glycogenolysis and gluconeogenesis), or bilateral adrenal haemorrhage (glucocorticoid insufficiency). It remains unknown whether treatment or avoidance of hypoglycaemia improves outcomes in critical illness.

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EP092

Case Series; Experience of the Management of 2 Patients with Severe Anorexia Nervosa in Sligo University Hospital using the MARSIPAN protocol

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Anorexia nervosa has the highest mortality of all psychiatric conditions. Sligo University Hospital (SUH) uses the MARSIPAN protocol for the (Management of Really Sick Patients with Anorexia Nervosa) for inpatient treatment.

Case 1; 22-year-old lady with a BMI of 12.06 kg/m^2, admitted voluntarily and reported food and bowels dominated her life, did not leave the house, consuming only nutritional 'supplements, laxatives. She was commenced on a naso-gastric feed at 10/kcal/kg/day, 1 litre fluid restriction, cardiac monitoring, confined to bed (commode for toileting), nursed one-to-one in an observation bay on a general medical ward. Electrolyte supplementation was required for refeeding syndrome. Although weak she displayed significant sabotaging behaviour, micro-exercising in bed, on her phone/computer. She continued to hold bowel and bladder for weighing. She remained in hospital for 63 days with gradual reintroduction of oral diet and exercise. 9 months post discharge she has a BMI 18.5 kgs/m^2 and a part-time job.

Case 2; 27 year old lady with 10 Ibs weight loss in 3 weeks eating only celery, BMI 13.0 kgs/m^2. The MARSIPAN protocol was commenced as above, allowing only vitamin supplementation orally. However she aspirated, developed pneumonia and respiratory failure requiring and mechanical ventilation and inotropic support and electrolyte supplementation for refeeding syndrome. Upon weaning sedation she commenced micro-exercising with limb movements, animated conversations, requests for opening of windows to shiver and lose calories. She remained in hospital for 83 days. 7 months post discharge she has a BMI of 16 kg/m^2 and is living independently.

As one of only 2 Specialist Eating Disorder Units in Ireland a protracted coordinated multidisciplinary approach has been successful in 14 such patients to date.

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EP093

An unsual case of erectile dysfunction with high total testosterone levels

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We report a case of a 56-year-old gentleman who presented to the endocrine clinic with erectile dysfunction. He had elevated SHBG levels, MCV, gamma GT, ferritin, iron and markedly elevated testosterone and transferrin saturation (GGT 167 IU/l, ferritin 1128 ug/l, testosterone 62.5 nmol/l). He had a marginally low platelet count (123X109/l). He denied ever taking testosterone supplements. His calculated free testosterone was normal. His full blood count was otherwise unremarkable. He had negative myeloma, viral and autoimmune screens. He had no history of diabetes with a normal OGTT. He drank 25 units of alcohol a week. His BMI was 30 kg/m^2. His US liver showed a fatty liver with splenomegaly. His pituitary MRI scan was normal. He was investigated by haematologists for hereditary haemochromatosis. HFE genetic screen was negative. JAK 2 mutation awaited. He has had one unit of venesection.

Discussion

This represents a rather unique presentation of a case with unexpectedly high total testosterone levels secondary to elevated SHBG levels, considering patient's high

Iron Studies	
Ferritin	1128 ug/l
Iron	44 umol/l
Transferrin saturation	86%

Pituitary Screen	
FSH	6.4 IU/l
LH	10 IU/l
Total Testosterone	62.5 nmol/l
SHBG	193 nmol/l
TSH	1.68 mIU/l
fT3	5.4 pmol/l
fT4	11.2 pmol/l
Prolactin	298 mIU/l
IGF-1	7.4 nmol/l
Short Synacthen test (nmol/l)	
Basal Cortisol	162
30 min	551
60 min	622

BMI with features of metabolic syndrome. The presentation is further complicated by hyperferritenemia which is thought to be secondary to nonalcoholic fatty liver disease (NASH). NASH and dysmetabolic iron overload syndrome have been shown to be associated with raised SHBG levels. Emerging evidence suggests that liver fat content rather than BMI is a strong determinant of circulating SHBG. Both metabolic syndrome and liver iron overload have been implicated in moderate hypogonadotrophic hypogonadism. However the high total and normal free testosterone levels with normal gonadotrophins in our patient precludes it as the cause of his erectile dysfunction. There are no similar clinical cases found in literature.

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Reproduction

EP094

Secondary amenorrhea due to abnormalities of the autosomal chromosomes – Case report

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Introduction
Follicle-stimulating hormone (FSH) and its corresponding receptor (FSHR) are essential factors for regular gonadal development, sexual maturation at puberty and gamete production during the fertile period in both sexes. The FSHR encoding gene was mapped to the short arm of chromosome (CR) 2 in 2p16.3.[3] In females, inactivating mutations result clinically – depending on the degree of inactivation – in primary amenorrhea, secondary amenorrhea or premature ovarian failure (POF).
We present the case of a 17 y.o. girl who presented in our clinic with secondary amenorrhea. She had only one spontaneous menstrual bleeding at the age of 15. She presented with spontaneous sexualisation corresponding to Tanner stage 5, had a normal neuropsychomotor development during childhood and didn't showed any dysmorphic signs. Bone age corresponded to the chronological age. Laboratory investigations confirmed hypergonadotropic hypogonadism with prepubertal estradiol levels: FSH 99.42 IU/l (follicular phase 3.5–12.5 IU/l), LH 42.34 U/l (follicular phase 2.4–12.6 IU/l), estradiol 21 pg/ml (follicular phase 27–122 pg/ml). Her prolactin and cortisol level, thyroid function, and beta HCG were in the normal range. Ovarian ultrasound didnt show any ovarian follicular development.
Karyotype analysis showed the presence of a translocation t(2;4) (2pter→4qter) in all studied metaphases with no other number or structure chromosome abnormalities detectable by G-banding. FISH-whole CR painting will be performed for CR 2 and 4. DNA sequencing and a CGH will also be performed for changes in the translocated sequence knowing that on the short arm of CR 2 is the region where both FSH and LH receptor gene and encoded.
No genetic testing was performed to the parents or other relatives.
Conclusion
Genetic causes occupy the first place in the etiology of premature/primary ovarian failure (POF). Not only abnormalities of the sexual CRs but also of the autosomal ones can lead to POF.

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EP095

Oligo-amenorrhoea – a triple whammy?

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A 20-year-old female first presented in 2013 with a six-month history of feeling faint, palpitations, weight loss and oligo-amenorrhoea. She was found to have autoimmune thyrotoxicosis with a fT3 15.2, fT4 43.3, TSH <0.05 and TPO antibodies strongly positive. She was subsequently commenced on Carbimazole 20 mg once a day and was biochemically euthyroid within 6 months. Interestingly, however, she continued to lose weight and remained oligo-amenorrhoeic. Her BMI was now 18 (weight 46 kg).
Her initial pelvic ultrasound did not show polycystic ovaries. Serum testosterone was 1.2 mmol/l, LH 0.9U/L, FSH 3.7U/L, oestradiol 161 pmol/l, prolactin 124 mU/L with 9am cortisol and remaining pituitary profile within normal range. MRI pituitary was unremarkable. Her TFTS remained within normal range off the Carbimazole. DEXA scan: *T*-score -0.2 at lumbar spine, -0.1 at left hip.
She was diagnosed with anorexia nervosa by the eating disorders team. With their support, she gradually gained weight from 46 kg in January 2014 to 54.3 kg in April 2015, 65 kg in September 2015 and now 73 kg in 2016 (BMI 30). However despite normalisation of her weight, spontaneous periods did not resume. Her repeat pelvic ultrasound showed ovaries that were a little bulky with several small peripheral follicles and were thought to be polycystic in appearance with a reverse FSH:LH ratio (FSH 7.1U/L, LH 9.3U/L, oestradiol 255 pmol/L, Prolactin 132 mU/L, TFTs normal) suggestive of PCOS. She has no immediate plans to start a family and is taking an oral contraceptive pill at present, with regular withdrawal bleeds. She has been given lifestyle advice to regain a normal weight.
This case highlights multiple diagnostic and treatment challenges in a young patient with oligo-amenorrhoea. It is proposed that her amenorrhoea may originally have been due to Graves' disease, was subsequently due to her persistent low body weight (hypothalamic amenorrhoea secondary to anorexia nervosa), and ultimately, after gaining excess weight, due to exacerbation of underlying polycystic ovary syndrome - a clinical conundrum?

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EP096

Triple X syndrome and premature ovarian insufficiency - A case report

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Abstract withdrawn.

EP097

Unusual presentation of sertoli cell only syndrome with extreme tiredness

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Sertoli Cell Only Syndrome (SCOS) is a rare cause of male infertility in which the cause is often unknown.
Here, we report an unusual presentation of SCOS in a 32 year old man with severe fatigue, flushing, aches and hypothyroidism. These symptoms did not improve despite correcting hypothyroidism with thyroxine replacement. There have been no features of depression and he has been investigated thoroughly as predominant fatigue has been affecting everyday life. Patient is married and has no children. Bedside observations and general physical examination is normal. Laboratory testing for anaemia, kidney function, Vitamin D, liver function, coeliac screen, vascuilitic screen and anti-acetylcholine-receptor-antibody is negative. Plain X-ray of chest is normal. Pituitary axis testing revealed raised Follicle Stimulating Hormone (FSH) of 34.4 IU/L (normal $<$ 8 IU/l), borderline Lieutinising Hormone (LH) of 8.5 IU/L (normal 3-8 IU/L), normal prolactin, normal levels of morning cortisol and normal Short Synacthen Test. His semen analysis confirmed Azoospermia. Patient is diagnosed with probable SCOS and is awaiting biopsy confirmation.
Treatment with a trial of Testosterone therapy is considered and we will have the outcome of this on patient's symptoms in due course.
There has been poor reporting of symptoms in SCOS except commonest investigating cause of infertility. We hope, via sharing this case and further discussions amongst experienced clinicians will help broaden our understanding of symptoms of SCOS.

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EP098

Siginificant hyperandrogenism in a postmenopausal woman from a likely ovarian source

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Introduction
The polycystic ovary syndrome is the commonest cause for hyperandrogenism in young women. However, in older women, adrenal and ovarian tumours are more common, particularly if (a) hyperandrogenism is of short duration, (b) causes significant clinical androgenisation, and (c) is biochemically severe. We present an elderly woman who presented diagnostic and therapeutic challenges on account of her comorbidities.
Case Presentation
A 67-year-old woman had a 4-month history of excessive hair growth and alopecia. She had COPD, diabetes mellitus, and peripheral vascular disease but didn't take offending medications. Clinically, she had significant facial, abdominal, and trunk hirsutism (Ferriman-Gallwey score 27), but no signs of Cushing's syndrome. She also had significant alopecia and temporal recession. Examination of her systems was normal. Investigations showed - Plasma testosterone - 46.8 and 50 nmol/l, DHEAS - 10 nmol/l, androstenedione - 7.5 nmol/l; 17 hydroxy progesterone (17HP) - 11.6 nmol/l; overnight dexamethasone suppression test – 9 am cortisol < 28 nmol/l; dexamethasone androgen suppression test - plasma cortisol.
Discussion
This patient presented with rapid onset, severe clinical and biochemical hyperandrogenism, suggesting an androgen secreting tumour. This was proved to be ovarian (androgen suppression test while awaiting selective venous sampling), and benign (lack of growth on interval scans 7 months apart) after investigations. She was unfit for surgery, and was therefore given cyproterone acetate with normalisation of androgen levels and clinical improvement.

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EP099

Extremely low HDL-C in a patient with premature ovarian failure: case presentation

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During menopause, plasma lipids change in an unfavourable way to a more atherogenic pattern with, increased total and LDL-cholesterol and decreased HDL cholesterol concentrations. Women with POI show increased cardiovascular morbidity and mortality regardless of the cause of the ovarian insufficiency. The treatment of premature ovarian failure in patients presenting extremely low HLD-C is a real challenge.
We present the case of a 29 years old patient who was referred to our clinic for secondary amenorrhoea, headaches and lower limb pain.
Laboratory investigations showed: Thrombocytopenia (80000/100000/ml), FSH = 173 mUI/ml, LH = 92 mUI/ml, Estradiol < 10 pg/ml, normal basal and stimulated cortisol, normal calcium and thyroid function, Cholesterol = 74 mg/dL, HDL-col = 3.8/< 3 mg/dL, LDL-col = 48.6 mg/dL, Triglycerides = 108 mg/dL, Non-HDL = 70.2 mg/dl, ApoA1 < 0.03 g/l (1.08–2.25) very low, ApoB = 0.93 g/l (0.6–1.17)- normal. She was started on contraceptive therapy with regular menstrual cycles with no improvement on the lipid panel (HDL-C remained < 4 mg/dl). The cardiological and neurological exams didn't show any signs of premature vascular disease. The haematology exam excluded artifactual or secondary causes of low HDL-C. The thrombocytopenia was defined as essential. Confirming the causes of POI and low HDL-C requires genetic testing which was not performed for financial reasons.
Cardiovascular risk assessment is not well defined in this situations. The association between extremely low HDL-C levels and atherosclerosis still remains unclear in genetic conditions, as well as in the context of POI. HRT would be a better option than monophasic contraceptives. Statin treatment must be individualised. The purpose of the treatment is prolonging the patient's life and improving the quality of life.
Causes of HDL-C below 20 mg/dl in the absence of severe hypertriglyceridemia are primary monogenic disorders (apolipoprotein A-I mutations, Tangier disease, and lecithin-cholesterol acyltransferase deficiency) or secondary causes (androgen use, malignancy).
Causes of premature ovarian failure are wide ranging: chromosomal and genetic defects (Turner syndrome, fragile-X syndrome, autosomal gene defects), autoimmune disorders, iatrogenic causes, environmental factors.

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Thyroid

EP100

Thymic hyperplasia in Graves' disease – wait and see, or intervene?

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Introduction
There is no consensus about the management of thymic enlargement in Graves' disease (GD). If imaging indicates 'benign' thymic appearances, and interval scans are stable, most authorities advocate no intervention until thyrotoxicosis is controlled. We present 3 patients with GD and incidentally found thymic enlargement.
Case presentations
a. A 37-year-old female presented acutely with osmotic symptoms, a weight loss of 5 stones and postural symptoms. She was dehydrated, had postural hypotension, a smooth goiter (with loud bruit), but no pigmentation. Investigations showed: free T3 > 46.1 pmol/L; free T4 59.5 pmol/L; TSH < 0.01 mU/L; TRAb 25.5; corrected calcium 2.98 mmol/L; PTH < 0.5 nmol/L; short Synacthen – cortisol 305 nmol/L (0 min) and 343 nmol/L (30 min); adrenal antibodies + ve. CT scans showed benign thymic enlargement. She was rehydrated, given pamidronate and GD and Addison's disease treated appropriately.
b. A 36-year-old female, was investigated for breathlessness and weight loss. CT showed an anterior mediastinal mass and she was scheduled for biopsy under anaesthesia. Investigations showed free T3 17 pmol/L; free T4 32 pmol/L; TSH < 0.02 mU/L and TRAb + ve. On review in the Thyroid clinic, the CT appearances were consistent with benign thymic hyperplasia. She was given carbimazole and surgery postponed.
c. A 47-year-old female presented with breathlessness, chest pain, weight loss and shakiness. CTPA showed benign thymic hyperplasia. Investigation showed free T3 6.7 pmol/L; free T4 18.7 pmol/L; TSH < 0.02 mU/L and TRAb + ve. Her GD was treated appropriately.

Discussion
The true incidence of thymic hyperplasia in GD is unknown but estimated to be 96–97%. Our patients had thymic hyperplasia discovered incidentally. Studies have shown regression in the vast majority of subjects, on treating GD. Therefore if CT appearances are 'benign' (an arrowhead appearance, linear margins, isodense with muscle, without calcification or infiltration), thymic biopsy or removal may be postponed till interval scans are done after the control of thyrotoxicosis.

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EP102

Persisting biochemical thyrotoxicosis due to biotin supplementation in a patient with Graves' disease

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A 46-year-old lady was referred to endocrinology with thyrotoxicosis. She was diagnosed with Graves' disease by her GP in October 2016 when presenting with classical symptoms and investigations [TSH < 0.01 mIU/L (NR 0.3–4.2), fT4 = 34.3 pmol/L (NR 9–23), TSHrAb > 30 u/mL (NR < 0.4), and increased iodine uptake]. She was therefore started on carbimazole 15 mg/day. She returned to her GP in December 2016 reporting resolved symptoms, however, she remained markedly biochemically thyrotoxic (fT4 = 34.6 pmol/L). Carbimazole was further increased to 20 mg/day and then 30 mg/day in view of the persisting biochemical thyrotoxicosis.
She was first seen in our clinic in May 2017 complaining of reduced energy and weight gain. On further questioning, she reported that due to initial hair loss at diagnosis she had been taking daily Biotin supplements, but had now stopped two weeks prior to this clinic due to cost. Interestingly, she was still clinically euthyroid but with normal free thyroid hormones for the first time (fT4 = 9.4 pmol/L). She was advised to remain off Biotin and reduce her carbimazole.

Herein, we present a case of Grave's disease treated with increasing doses of carbimazole despite clinical resolution, due to persisting biochemical thyrotoxicosis as a result of Biotin assay interference. Following cessation of Biotin in May 2017, her true thyroid biochemistry was revealed. Many laboratories use immunoassays to measure analytes through biotin-streptavidin interactions. High levels of serum biotin can lead to false apparent biochemical thyrotoxicosis. Laboratories are aware of such interactions; however, most clinicians are unaware. Doctors are heavily dependent on laboratory testing and false results can lead to great harm without awareness of assay interactions. These could include overtreatment with carbimazole or even unnecessary radioiodine or thyroidectomy. Therefore, in view of the increasing use of over-the-counter supplements, recognition of this biotin interaction must be highlighted to endocrinologists and directly looked for when taking a history.

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EP103

Severe thyroid-associated orbitopathy manifesting two years post total thyroidectomy for follicular carcinoma variant of the thyroid

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We present a case of severe thyroid-associated orbitopathy in a 44-year-old man with metastatic follicular carcinoma of the thyroid. He presented with a neck lump, and following further investigations, underwent a hemithyroidectomy followed by a completion thyroidectomy. Histology of the thyroid confirmed widely invasive follicular carcinoma of Hurthle cell type with foci of vascular invasion (pT3 Nx Mx). He received radioactive iodine ablation therapy (3.7GBq), and continued on suppressive Levothyroxine therapy.

He remained clinically stable for 24 months, when he was discovered to have relapsed (thyroglobulin 290 ug/L, thyroglobulin antibody <20 IU/ml). Cross-sectional imaging and a diagnostic Iodine-123 imaging showed active disease in subcarinal and mediastinal lymph nodes, liver, lungs and skeletal system. Therapeutic radioactive iodine (5.5 GBq) was administered, with variable uptake within the thyroid bed and paratracheal region, anterior mediastinum and liver.

Five months later, he reported a three-month history of orbital discomfort and visual disturbances. Clinical examination, biochemistry (TSH receptor antibody >30 unit/ml) and magnetic resonance imaging were consistent with features of moderately active thyroid-associated orbitopathy with no sight threatening complications. There is no personal or family history of autoimmune thyroid or other autoimmune disease. He was commenced on a 12-week course of pulsed intravenous Methylprednisolone, with only slight improvement. He continued to receive concurrent palliative treatment for his metastatic disease including Zoledronic Acid, Sorafenib (tyrosine kinase inhibitor) and single fraction radiotherapy to bone metastases. As he continued to have severe restriction of upward gaze and bilateral marked lid retraction, he received external beam orbital radiotherapy (20Gy in 10 fractions). His metastatic disease remained active and he died 17 months after his relapse.

We postulate an unusual and large antigen load precipitating thyroid-associated orbitopathy in the absence of endogenous TSH production following radioactive iodine therapy and prior to the use of an immune checkpoint inhibitor (Sorafenib).

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EP104

Thyroid FDG-PET positivity; Pattern and implications

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Use of 18F-FDG-PET/CT (PET) staging for a variety of malignancies has increased in recent years. A rise in detection of incidental thyroid lesions creates a novel diagnostic challenge. We present four cases of Thyroid PET positivity.

A 62-year-old lady with pulmonary adenocarcinoma on contrast CT-Thorax had diffuse thyroid PET uptake. Biochemistry revealed a self-limiting TSH rise. Thyroid ultrasound showed benign nodular goitre (U2). Findings may have represented contrast-induced thyroiditis. Patient was referred for curative pulmonary upper lobectomy.

A 62-year-old gentleman with oesophageal adenocarcinoma had PET staging showing focal uptake within a right thyroid nodule. Thyroid biochemistry was normal. Ultrasound revealed a goitre with a U3 nodule right of the isthmus. Right thyroid lobectomy and isthmusectomy was undertaken. Histology confirmed a follicular variant of papillary carcinoma.

A 78-year-old lady undergoing work-up for pancreatic intraductal papillary mucinous neoplasm and lung cancer was found to have a PET-positive left thyroid nodule. Thyroid biochemistry and calcitonin were normal. Ultrasound with FNA showed a U3 nodule and Thy1 cytology respectively. Diagnostic left lobectomy was performed; histology showed a follicular adenoma.

A 42-year-old lady had a right lower lobe lesion on chest x-ray. Staging CT revealed a thyroid isthmus nodule with focal PET-positivity; lung lesion was benign. Thyroid Ultrasound revealed a U3 nodule; FNA suggested Thy3f cytology. Patient was referred for diagnostic thyroid lobectomy.

Incidental PET positive thyroid lesions present a diagnostic challenge when discovered alongside other malignancies requiring urgent staging investigations and treatment. The pattern of thyroid uptake appears indicative of the underlying aetiology. From published data, the risk of malignancy with focal uptake is between 23%–35%. Diffuse thyroid uptake is usually benign. A standardised approach to promptly evaluate PET-positive thyroid incidentalomas is needed for timely management of these patients.

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EP105

A case of Graves' disease refractory to radioactive iodine

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We report a rare case of hyperthyroidism secondary to Graves' disease which failed to respond to three consecutive therapeutic doses of radioactive iodine 131. This 62 year old gentleman with a history of ischaemic heart disease was first referred to endocrine services in September 2014 with classical symptomatic hyperthyroidism. He described fatigue, significant weight loss of 3.5 stones, sweating, palpitations and heat intolerance over a three month period. On examination he had a moderately enlarged, symmetrical, non-tender goitre and no ophthalmopathy. Blood tests confirmed hyperthyroidism (TSH <0.05 mU/L, fT4 47 pmol/L, fT3 23.5 pmol/L) with positive autoimmune indices (TBII 10.4 U/L). Ultrasound scan suggested multiple thyroid nodules, however uptake was uniform (although not high) on isotope scanning confirming Graves' disease.

After a year of titrated carbimazole therapy he elected for treatment with radioactive iodine I-131 and was administered 489 MBq. He relapsed within six months and re-presented in atrial fibrillation with severe left ventricular diastolic dysfunction on echocardiogram. Interestingly, TBII level was now markedly raised at >100 U/L. A second dose of radioiodine (499 MBq) was administered at 8 months, followed by a third (664 MBq) four months later when this was unsuccessful, resulting eventually in hypothyroidism.

Now nine months after completing treatment he has developed T3 toxicosis (TSH <0.05 mU/L, fT4 18 pmol/L, fT3 9.3 pmol/L) indicating a third relapse.

Radioiodine renders 60–90% of patients euthyroid or hypothyroid after the first treatment. We describe a very rare case which has failed to respond after three. Multiple factors have been associated with poor patient response, and in this case male gender, large goitre, high TBII and relatively low iodine uptake may all be contributing.

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EP106

Hyperthyroidism secondary to weight loss supplements

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Case History

A 26 year old female patient was referred to her local endocrine clinic having presented to her GP complaining of ankle swelling. Routine biochemistry revealed a suppressed TSH (<0.05 U/l), and reduced serum levels of free T4 (2.0 pmol/l) and T3 (3.2 pmol/l). Random serum cortisol measurements were also elevated on 2 separate occasions (1266 nmol/l and 991 nmol/l). Clinical examination revealed her to be clinically euthyroid with no evidence of glucocorticoid excess, and no visual field defect was noted.

Investigations

The patient had normal 24 hour urinary steroid profile, and 8am cortisol suppressed to 42 nmol/l during an overnight dexamethasone suppression test.

Serum prolactin and GH were also within the normal reference ranges. LH and FSH were fully suppressed as the patient was taking a combined oral contraceptive pill. MRI pituitary was reported as normal.
Results and Treatment
A diagnosis of secondary hypothyroidism was made. Levothyroxine was commenced at a dose of 50 mcg daily. The patient was reviewed after 8 weeks, and FT4 was within the normal range at 12.2 pmol/l, with TSH remaining suppressed. The patient was reviewed 4 months later, by which point she was complaining of heat intolerance and hair loss. Thyroid biochemistry was as follows: TSH <0.05, FT4 8.4 pmol/l, T3 44.0 pmol/l. On further questioning, it became apparent that the patient had been regularly ingesting a number of supplements to aid weight loss.
Conclusions
This case illustrates the potential for inadvertent thyroid hormone ingestion, in patients using 'energy' and 'weight loss' supplements. In this case, regular ingestion of T3 may have led to a biochemical picture mimicking secondary hypothyroidism.

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EP107

A case of clinical parotitis following radioiodine treatment for toxic multinodular goitre

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Radioactive iodine is used routinely and safely in the treatment of hyperthyroidism. We describe an unusual side effect after a single treatment in a patient with subclinical hyperthyroidism.
A 64 year old woman was referred to our service with multinodular goitre. She was found to have subclinical hyperthyroidism with TSH 0.17 mU/L, fT3 5 pmol/L and fT4 14 pmol/L. She underwent radioactive iodine treatment with 530 MBq of Iodine -131 in January 2017. Two weeks following this she developed left sided facial swelling with difficulty chewing. Clinical examination revealed a tender, swollen parotid gland. This settled over the following two weeks and subsequent ultrasound demonstrated no focal salivary gland abnormality. The clinical diagnosis was therefore of radiation parotitis. On further questioning she has occasional bursts of increased salivary flow since, but no xerostomia or chewing difficulties.
Iodine-131 is a beta emitting isotope of iodine used intravenously or orally for the treatment of hyperthyroidism and thyroid cancer. Studies in cancer patients have demonstrated that I-131 is taken up avidly and concentrated by salivary gland tissue, particularly the parotid gland. Sialoadenitis is a recognised complication of therapy in these patients, as well as longer term problems with xerostomia and dental caries, however this has been reported following doses of 150–200 MCi (5550-7500 MBq). To our knowledge there have been no reports of sialoadenitis following standard therapy for hyperthyroidism (400–800 MBq). Given that this toxicity is dose related, milder abnormalities may go un-noticed. We should therefore consider enquiring about symptoms of salivary gland dysfunction as part of routine post radioiodine follow up, particularly for patients with higher or repeated dosing, in order to protect patients from longer term oral health problems.

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EP108

Development of Graves' ophthalmopathy post-thyroidectomy: Important lessons for clinical practice

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A 73-year-old lady presented with symptoms of weight-loss, tiredness, sweating and thyroid gland enlargement. Biochemistry demonstrated a T4 of 65.7 pmol/L and TSH <0.02 mmol/l. TSH receptor antibodies were positive confirming Graves' disease. Thyroid ultrasound demonstrated reduced echogenicity and increased vascularity with a 3.2 cm left lobe U3 nodule and FNA planned.
The patient developed a severe reaction within 17 days of starting carbimazole, with widespread urticarial rashes and joint pain. She was reluctant to initiate propylthiouracil due to risks of similar drug reactions. Based on medication concerns and the U3 nodule, a thyroidectomy was performed after a short pre-operative propylthiouracil & propranolol course. The patient reported no eye symptoms at any point prior to, or immediately following thyroidectomy.
Three months post-thyroidectomy she developed bilateral eyelid erythema, periorbital swelling and vertical diplopia. Ophthalmology confirmed Graves' ophthalmopathy. High dose methylprednisolone and oral prednisolone was prescribed, improving the eye disease significantly.
Graves' ophthalmopathy is known to precede or follow endocrine features of thyrotoxicosis, typically occurring within 18 months of each other (1). Graves' ophthalmopathy is likely caused by an autoimmune retrobulbar tissue reaction to thyroid stimulating hormone receptor antibodies prompting orbital fibroblast proliferation (2). Thyroidectomy significantly reduces Thyroid-stimulating hormone receptor autoantibioidy levels (3). The new development of Graves ophthalmopathy following thyroid surgery is rare. A retrospective Swedish study reports it to occur in just 1% of patients (4), however the duration of thyroid disease prior to surgery is not reported.
This case highlights a rare example of Graves' ophthalmopathy developing months after thyroidectomy. It is important that such a risk is explained to patients when consenting for surgery, as they may otherwise expect to be completely cured. Furthermore it is essential community and specialist healthcare professionals are aware of possible late development of Graves' ophthalmopathy following thyroidectomy and refer for appropriate assessment without delay.

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EP109

Thymic hyperplasia associated with Graves' disease: could thymic surgery be deleterious?

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Thymic hyperplasia is frequent in patients with Graves' disease (GD) but it rarely is large enough to be detected radiologically as an anterior mediastinal mass. In the few cases operated, lymphoid hyperplasia (i.e. lymphoid follicle proliferation with expansion of both the cortical and the medullary component) has been documented histologically in 38% of cases, while true thymic hyperplasia, i.e. thymic enlargement with normal tissue architecture, was found more rarely. In only 4 out of 107 patients with GD a malignant thymic tumor was reported.
The mechanisms of this association remain unclear, both autoimmunity and hyperthyroidism being a potential cause. Hyperthyroidism persists after thymectomy but the treatment of hyperthyroidism with antithyroid drugs usually results in a decrease of the thymus.
We describe the evolution of 3 patients with GD and thymic mass on the computed tomography. In 2 patients, a 49 year-old female and a 28 year-old male, the thymic mass (3.3/1.6 cm and 5.5/2.5 cm, respectively) shrinked to normal after 4 and 6 months of treatment with methymazole. In the 3rd patient, a 37 year-old female, the thymic mass 4.8/3.7 cm persisted after 5 months of treatment with methymazole (TSH normalization was obtained only in the last 2 months). She underwent thymic surgery; the pathological exam showed thymic lymphoid hyperplasia. Two months later, the patient had overt myasthenia gravis with antibodies to acetilcholine receptor and required treatment with glucocorticoids and pyridostigmine. She was diagnosed 2 years later with seronegative rheumatoid arthritis and systemic lupus erythematosus. Her GD was cured after 2.5 years of medical treatment, with persistence of TPOAb. It is debatable if the thymus removal or a severe autoimmune background was the cause for this unfavorable evolution.
Conclusion
When thymic hyperplasia is diagnosed in association with GD, in the absence of myasthenia gravis and/or suspect CT findings, only antithyroid treatment and radiological follow-up are indicated. Thymic surgery may carry unnecessary risks for these patients.

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EP110

Challenges in management of a severe case of Amiodarone induced thyroiditis type 2

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Amiodarone-induced thyroiditis (AIT) can be a diagnostic and therapeutic challenge. It can be a diagnostic challenge in clinical cases, where response to therapy can be slow. It is important to achieve an early differentiation between various subtypes (i.e. AIT type 1 or AIT type 2) to guide therapy. We present a case of a 51-year-old man with a history of paroxysmal atrial fibrillation for which he was treated with a maintenance dose of Amiodarone. He presented with a two week history of progressive breathlessness and lethargy. He had no relevant past medical history or family history of thyroid disease. On presentation he was in atrial fibrillation and had bilateral tremors, an altered mentation, visible goitre and profuse sweating. His initial investigations demonstrated a free T4 of 70 pmol/l and his TSH was undetectable (<0.02 mU/L). His thyroid ultrasound showed decreased vascularity and no uptake on thyroid uptake scan. His Amiodarone was withheld and he was initiated on anti-thyroid treatment with Carbimazole, beta-blockade and oral steroids. He responded initially well to the above therapy, but required incrementation in dosage of his Carbimazole when he relapsed at 2 weeks post-treatment (increase in free T3 levels i.e. 20 pmol/L). His free T4 and T3 levels have normalized 4 months after close monitoring, requiring high dosage of Carbimazole and oral steroids. This case highlights the importance of earlier identification, differentiation between various subtypes of AIT and treatment of this potentially life-threatening condition, which can potentially progress towards a thyrotoxic storm or culminate in thyroidectomy if unresponsive to therapy. Discontinuation of therapy is guided by close follow up surveillance, monitoring free T3 levels and a thyroid uptake scan at 6 months.

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EP111

Nivolumab induced thyroid dysfunction in a 61 year old male with non-small cell lung cancer (NSCLC)

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Background
Nivolumab is a programmed death receptor-1 blocking antibody and the first to gain regulatory approval for use in non-small cell lung cancer (NSCLC). Whilst well tolerated in clinical trials, 3% of patients in a phase Ib study displayed thyroid dysfunction. Diagnosis and referral to appropriate specialties is a challenge in complex cancer cases where symptoms are often multi-factorial. Improved knowledge of the potential complications of new and novel cancer treatments is, therefore, of utmost importance.
Case presentation
Here we present a patient, RS, who developed thyrotoxicosis and subsequent hypothyroidism following Nivolumab treatment. RS is a 56 year old male with T4N2M0 NSCLC (likely squamous) first diagnosed in 2014 and initially treated with radical chemoradiation to good effect. Unfortunately, his disease re-presented in September 2016 and he was considered an ideal candidate for Nivolumab by the oncology team. First cycle was initiated in November 2016 and the treatment was well tolerated with only lethargy and fatigue as symptoms. Following the 3rd cycle of therapy, he was found to be thyrotoxic (free T4 of 54, TSH of 0.03), and had positive anti thyroid peroxidise antibodies but negative thyroid receptor antibodies. Nivolumab was withheld at this point. Following cessation, T4 levels decreased and Nivolumab was recommenced. However, he has remained hypothyroid following initial thyrotoxicosis both with and without Nivolumab treatment. He requires a low dose of levothyroxine to keep clinically symptom free.
Conclusions
The management of induced endocrine disorders following chemotheraphy/-immunotherapy treatment can be difficult due to vague symptoms and a generalised malaise often induced by the treatment itself. Careful blood monitoring is essential in spotting and acting on such side effects especially when rare as in this case.

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EP112

Delayed diagnosis of severe secondary hypothyroidism in a patient presenting with mixed hyperlipidaemia and metabolic myositis

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Clinical Case
A 51 year old woman of south Asian descent was referred by her GP to outpatient endocrine clinic for assistance with her mixed hyperlipidaemia (*Cholesterol 9.5 mmol/L, HDL Cholesterol 1.03 mmol/L Triglycerides 6.7 mmol/L*). Her past medical history included a previous hemithyroidectomy for removal of a thyroid nodule (histologically benign) and obesity.
The patient's symptoms were of weight gain (5 kg in 18 months), mild lethargy and widespread aches and pains.
The patient was found to have a persistently elevated Creatine Kinase (*995 – 1950 Ui/L* [24 – 170]) with a normal autoimmune screen.
Serial TSHs since the hemithyroidectomy had been within reference range (*2.17 to 3.26 mUi/L* [0.4 – 4.5]). However, when thyroid hormones were measured directly the patient was found to be profoundly hypothyroid (*Free T4 1.7 pmol/L* [12.3 ? 20.2], *Free T3 1.3 pmol/L* [3.7 – 6.7]).
Further work-up was suggestive of combined anterior pituitary hormone deficiency (09:00 Cortisol 195 nmol/L, IGF-1 2.4 nmol/L, Prolactin 9 mU/L, FSH and LH were inappropriately low as post-menopausal). A subsequent MRI brain revealed an empty sella.
Following thyroid and steroid hormone replacement there was a complete resolution of the metabolic myositis (*latest CK 139 Ui/L* [24 – 170]) and significant improvement in her lipid profile.
Conclusion
This is a case of a patient with severe secondary hypothyroidism presenting with a metabolic myositis and secondary hyperlipidaemia. This went undiagnosed in primary care for almost two years with false reassurance being provided by normal TSH values.
This case highlights an atypical presentation of severe hypothyroidism. It also highlights the importance of sending a T4 in addition to TSH when hypothyroidism is clinically suspected as per British Thyroid Society guidelines.

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EP113

A case of thyrotoxic hyperemesis

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Hyperthyroidism is associated with multiple gastrointestinal (GI) symptoms including vomiting, although this is not very common. We present a case of a 61-year-old female patient, who was admitted under surgeons with persistent and severe vomiting which was very difficult to manage. No acute surgical cause for vomiting was found and the patient was referred for a gastroscopy which was normal. Her past history was significant for Grave's disease which was in remission for last 20 years. On checking her thyroid function tests, she was grossly thyrotoxic with fully suppressed TSH.
Hyperthyroidism is frequently associated with GI symptoms such as diarrhoea, hyperphagia etc, however, vomiting is less common and can mislead clinicians to an alternate diagnosis. Therefore, the possibility of hyperthyroidism should be considered in cases of refractory unexplained vomiting, especially when there is past history of thyroid dysfunction.

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EP114

An interesting case of cryptogenic stroke in the setting of Graves' disease

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Background
Ischemic stroke is an unusual but important complication of Graves' Thyrotoxicosis that is induced by the hypoercoaguable state of thyrotoxicosis.

We present a 24-year old female patient admitted with a 3-day history of intermittent slurred speech associated with numbness of the right side of her mouth and face preceded by left sided headache.

She had a history of uncontrolled Graves' disease secondary to noncompliance. Following on her last outpatient endocrine follow up; there was a plan for definitive treatment in the form of radioactive iodine.

She is a smoker of and a teetotaller. She has been on the combined contraceptive pill up until one week prior to presentation.

On examination, she was tachycardic with a normal blood pressure and a blood glucose of 7 mmol/l. She had mild dysarthria and right facial droop but no other focal neurological deficit. CT on admission showed a possible left frontal lobe infarct which was subsequently confirmed on MRI scan.

ECG showed sinus rhythm and her thyroid function test indicated uncontrolled thyrotoxicosis with a Free T4 of 22.5 pmol/L and a fully suppressed TSH.

The overall impression was that her stroke was likely cardioembolic in origin, probably due to thyrotoxicosis-induced atrial fibrillation. However we were unable to capture the atrial fibrillation during the admission and on a subsequent 24 hour tape. The decision was to anticoagulate with Apixiban even in the absence of documented paroxysmal atrial fibrillation.

Her dysarthria improved and she was discharged on a high dose of Carbimazole together with propranolol and Apixiban.

Investigations including a Carotid Doppler and Echocardiogram were both normal. A young stroke screen was performed including a vasculitic screen were all within the normal range.

Conclusion

Whether patients with thyrotoxic atrial fibrillation should be anticoagulated remains controversial and needs further evidence.

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Featured Clinical Cases

Featured Clinical Cases

CC01

Novel *ABCC9* mutation with Cantu syndrome-associated phenotype of hypertrichosis with acromegaloid facial features (HAFF) with coexisting familial pituitary adenoma

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Pseudoacromegaly or acromegaloidism is used to describe cases where acromegaly-related physical appearance can be observed without any abnormality in the growth hormone (GH) axis. Acromegalic features, in particular coarse facies, together with hypertrichosis, are typical manifestations of one of the pseudoacromegaly conditions: hypertrichosis acromegaloid facial features (HAFF) syndrome. This condition phenotypically overlaps with Cantu syndrome and acromegaloid facial appearance (AFA) syndrome.

We present a three-generation family with five affected members with Cantu/HAFF syndrome, displaying marked acromegalic facies and prominent hypertrichosis, due to a missense mutation in the *ABCC9* gene. The proband, a girl aged 2 years-old, was referred to the Dermatology department due to marked generalised hypertrichosis, soon noticed after birth, in association with coarsening of her facial appearance. Her height was just below the 97th centile, and her endocrine assessment, including GH axis, was normal. Proband's father, paternal aunt and half sibling were referred to the Endocrine department for formal exclusion of acromegaly, they also had hypertrichosis. While GH axis was normal, two of them have non-functioning pituitary macroadenomas, a feature that has not been previously associated with Cantu/AFA/HAFF syndromes. The proband's father had recurrent pericardial effusions; cardiac involvement is known to be present in Cantu syndrome.

Activating mutations in *ABCC9*, and less commonly in the *KCNJ8* gene, two subunits of a ATP-sensitive potassium channel, have been linked with these conditions. There is no clear explanation for the mechanism acromegaloid features/hypertrichosis by activation of this channel. Remarkably, however, minoxidil, a well-known ATP-sensitive potassium channel agonist, can cause similar phenotype of hypertrichosis and acromegaloid facial features. This family raises awareness for this complex group of conditions, in particular endocrinologists and paediatric endocrinologists, who are likely to be referred to adult or paediatric endocrinologists as part of evaluation for acromegaloid features. The link with pituitary adenomas is currently unclear.

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CC02

A case of giant prolactinoma with JAK 2 positive mutation

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We present the case of a 19-year old male who presented with a generalized tonic clonic seizure associated with visual loss. Examination revealed severe visual field defects and arrested pubertal development. Laboratory evaluation revealed a very elevated prolactin of 298 410 mU/l, hypogonadotrophic hypogonadism, secondary adrenal insufficiency, and secondary hypothyroidism. He was also found to have thrombocytosis due to JAK 2 essential thrombocythaemia. Pituitary MRI revealed a large pituitary macroadenoma (58×40×28 mm) exerting significant pressure on the optic chiasm, associated with acute hydrocephalus. X-rays of the hands and wrist revealed delayed bone age of 16 years. The patient was diagnosed with a giant prolactinoma. Treatment was initiated with cabergoline 0.5 mg daily, hydrocortisone 5 mg BD, thyroxine 75 mcg daily and testosterone 100 mg IM injection every 4 weeks. Despite an impressive and rapid reduction in tumour size and prolactin levels, the visual defects and hypogonadal axis have not recovered after 24 months of therapy. Giant prolactinomas represent 0.5% of all pituitary adenomas (1). They are characterised by their size (>40 mm) and extremely high prolactin levels. The most common presentations include visual field defect, headache and sexual dysfunction, often accompanied by hypopituitarism (1). The goals of treatment are to relieve acute compressive symptoms, reduce tumour mass, normalise prolactin levels, and preserving pituitary function (2). Dopamine agonists are first line therapy for giant prolactinomas and can rapidly decrease tumour size and prolactin levels. Give his age, he will undergo testing for AIP and MEN mutations. Prolactin belongs to family of cytokines using the JAK-STAT signal transduction pathway, which regulates cellular proliferation and apopotosis (3). Constitutional activation of JAK2/STAT 5 pathway has been implicated in variety of tumours, however there has no previous account of lactotroph proliferation. We report the first case of JAK2 mutation in association with giant prolactinoma.

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CC03

A novel variant in the androgen receptor gene causing familial mild androgen insensitivity syndrome

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Introduction

Androgen insensitivity syndrome (AIS) is a heterogeneous condition. At the milder end of the clinical spectrum, patients with mild AIS (MAIS) are phenotypically male, and may present with infertility, either isolated or associated with gynaecomastia or signs of mild undervirilization. Most cases of complete and approximately 25% of partial AIS patients harbour mutations in the androgen receptor (*AR*) gene. Over 1,000 pathogenic variants have been described, but only approximately 40 of these are reported to cause MAIS.

Case report

A 30 year-old male with a history of infertility was referred to us following the finding of severe oligozoospermia and a raised testosterone. He had scant facial and body hair and gynaecomastia since puberty. His brother (who was also found to have oligozoospermia), and a male cousin from his mother's side had similar physical appearance. On examination, testicles were of normal volume (15 ml) and penile length was normal. Biochemistry showed raised testosterone (43 nmol/l, normal 8.6–29), raised LH (12 U/l, normal 1.7–8.6) and normal FSH (6 U/l, normal 4.6–12.5), with an increased androgen sensitivity index (516 U*nmol/l^2, normal 14.6–249.4). In view of these results and the putative family history, MAIS due to an *AR* mutation was suspected. Sequencing of the *AR* gene showed a novel hemizygous six base pair duplication resulting in the duplication of two amino acids (p.Leu56_Leu57dup). The same variant was identified in his brother and cousin. While this variant has not been previously reported, duplication of Leu57 was described in a subject with MAIS, further supporting the pathogenic role of the p.Leu56_Leu57dup variant.

Conclusion

We report a case of familial MAIS due to a novel, likely pathogenic variant in the *AR* gene. Considering its clinical presentation, MAIS is an underdiagnosed condition. Evidence of raised testosterone and a positive family history may guide the diagnosis and help identifying the causative genetic abnormality.

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CC04

Renin assay interference may conceal the diagnosis of primary aldosteronism

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Context

Primary aldosteronism (PA) accounts for 5–10% of all hypertension and 20–25% of refractory cases. Diagnosis is important as PA is associated with increased morbidity and mortality compared with 'essential' hypertension, and up to 50% of patients may benefit from unilateral adrenalectomy. Screening requires measurement of plasma renin activity (PRA) or concentration (PRC), and plasma aldosterone concentration (PAC), to yield an aldosterone:renin ratio (ARR). The finding of low plasma renin and raised ARR triggers further investigation.

Case
A 70-year-old man, with hypertension, hypokalaemia, suppressed PRA and markedly raised ARR, was referred to our centre for further investigation. However PRC, in the absence of confounding medications, was not consistent with PA. Suspecting an erroneous PRC result, we measured PAC (526 pmol/l), PRC and PRA on an independently drawn sample, which confirmed markedly divergent findings (PRA <0.2 nmol/l per hr (reference range (RR) 0.5–3.1); PRC 57 mU/l (RR5.4–60)), yielding strongly positive and strongly negative ARR screening respectively: PRA-derived ARR >2630 (RR <750); PRC-derived ARR 9.2 (RR <84). Further analysis revealed non-linear dilution of PRC, and polyethylene glycol precipitation was consistent with antibody interference, confirming PRC estimation to be unreliable in our assay. Moreover, repeat testing using an alternative PRC immunoassay platform demonstrated a PRC consistent with both the PRA result and a diagnosis of PA (PRC 5.5 mU/l (RR 11-32), ARR 95.6 (RR <84)). The patient proceeded to ^{11}C-metomidate PET-CT, with the demonstration of bilateral nodular adrenal disease, which has responded well to mineralocorticoid receptor antagonist therapy.
Conclusion
This is the first reported case of PRC assay interference. As measurement of renin concentration (mass) is increasingly used to screen for PA, clinicians should be alert to this possibility, especially when a clearly measurable renin result, seemingly ruling against PA, is discordant with the clinical context.

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CC05

Mutational analysis and SDHB immunostaining in bladder paraganglioma

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Bladder Paragangliomas (PGLs) constitute $<1\%$ of all bladder tumours and 5% in our patient cohort of 80 patients with tumours due to SDH deficiency. They often display an aggressive phenotype with metastatic disease and require long-term follow up. SDHB immunostaining plays a significant role in initial risk stratification and facilitating appropriate genetic testing. We present four cases of bladder PGLs; two with SDHB mutation, one SDHA and one is awaiting extended genetic analysis in view of young age (33 years). Our patients ranged from 29 to 67 years of age (median 42 years), 2M and 2F with predominant presentation being haematuria. Headache and sympathetic symptoms during micturition were also present in two patients. Plasma normetadrenaline was elevated in three patients and urine dopamine was also elevated in one who tested positive for SDHB mutation and subsequently developed metastatic disease. Initial biochemistry was not available in one patient as he underwent tumour resection in another centre several years ago. The tumours in all four patients displayed MIBG avidity although they are reported to have preference for FDG-PET and Gallium Dotatate. SDHB immunostaining is currently available in one patient only (67 year old lady) who tested negative in our initial routine genetic panel. However, she underwent screening for SDHA as the tumour sample repeatedly stained negative on SDHB immunohistochemistry indicating a likely mutation. SDHA frameshift variant Exon 2 c.133_136delinsCCT was detected which has not been previously reported in bladder PGLs. We conclude that SDHB immunostaining still remains an indispensable tool especially for the evaluation of bladder paraganglioma. As new causative genes become validated repeat testing should be performed in patients with a previously negative genetic panels and SDHA should be routinely included in the evaluation of the patient with a bladder PGL.

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CC06

Activating mutation in the arginine vasopressin receptor AVPR2 resulting in nephrogenic syndrome of inappropriate antidiuresis in a female

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Introduction
Hyponatraemia is the commonest electrolyte disturbance, but is not common in young people. Here, we describe a female subject, with recurrent unexplained symptomatic hyponatraemia in whom we considered the possibility of an activating mutation in the arginine vasopressin receptor type 2 (AVPR2) as a rare cause of Syndrome of Inappropriate Anti-Diuresis (SIAD).
Case
A 39 year old woman had a history of unexplained hyponatraemia (serum sodium typically 125 mmol/l) from the age of 16 years, clinically and biochemically consistent with SIAD(H). Adrenocortical and thyroid function, an acute intermittent porphyria screen and relevant imaging were normal and there were no culprit drugs. A water load test was performed which was suggestive of SIAD as she could excrete only 40% of a 20 ml/kg oral load by 240 min post-ingestion. Normal subjects excrete 78–82% of the water load in 4 hours. However, concentrations of copeptin, a stable and easily measured peptide which can be used as a surrogate marker of AVP release were low throughout the test (T, p.(Arg137Cys). Her mother was identified as a gene carrier and retrospectively she also gave a history of intermittent asymptomatic hyponatraemia. The proband is currently managed with fluid restriction of between 1.0 and 1.5 L/day preventing further admissions.
Conclusion
Unexplained hyponatraemia in young subjects should be investigated thoroughly and activating AVPR2 mutations considered in the differential diagnosis. This is an X-linked recessive disorder and all reported adult index cases to date have been males. Although two affected female carriers have been described presenting acutely in the neonatal period, this case represents the first reported adult female proband. A plausible explanation for this unusual presentation in a female could be skewed X-inactivation. Further genetic testing is awaited.

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CC07

Case report of MAX mutation causing bilateral phaeochromocytoma

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Background
Patients with Phaeochromocytomas (PCC) have been found to carry germline mutations in 40% of cases. The number of known susceptibility genes has risen sharply in recent times, from six to sixteen since 2009. We present a patient who was found to have a mutation in Myc Associated Protein X (MAX), one of the newly identified inherited susceptibility genes.
Case Presentation
A 16-year-old female presented with paroxysmal episodes suggestive of catecholamine excess and a seizure with labile blood pressure. Subsequently, a PCC was identified in the right adrenal gland which was later removed. Ten years later, follow up showed high urinary noradrenaline levels and a PCC was confirmed in the contralateral gland. Following a left adrenalectomy, genetic testing showed no mutation in any of the known susceptibility genes at the time. However, twelve years later repeat genetic testing identified a mutation in the MAX gene.
Discussion
MAX is a tumour suppressor gene involved in the MYC pathway and is mutated in approximately 1.12% of PCC cases. Current guidance states that the decision for genetic testing should be driven by the clinical features that the patient presents with e.g. bilateral disease, young age and a family history. Testing of the different susceptibility genes should be done depending on the location of disease and specific hormonal production. Our case illustrates the importance of repeat genetic testing to identify germline mutations in genes which at the time of presentation had not been linked to the patient's condition. Identification of patients with germline mutations is important as it enables the early diagnosis and treatment of relatives. This is especially advantageous if family members can be identified prior to metastasis, which occurs in 10% of MAX mutated cases.

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CC08

Pseudohypervitaminosis D due to assay interference

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Assay interference with various laboratory measurements has been reported in the presence of paraproteins. We report a case of a 57 year old woman, who was referred to endocrine clinic after being found to have elevated total vitamin D levels of 369 and 336 nmol/l (normal 50–100 nmol/l). She was not known to be on any Vitamin D supplements that could account for such high levels. Around the time of referral, she was also diagnosed with IgM paraproteinaemia. Therefore, possibility of assay interference that could cause pseudo-hypervitaminosis D was suspected. Vitamin D levels were repeated using a different assay system, using Tandem Mass Spectrometry method instead of Siemens, which had given elevated levels initially. The levels using Tandem Mass Spectrometry were 44 nmol/l (D3-38 nmol/l & D2 – 6 nmol/l) done on the first sample and repeat test done 8 weeks later was 22 nmol/l (D3-22 nmol/l & D2- <5). These levels suggested that she was infact Vitamin D deficient as the normal range using this analyser was >75 nmol/l. Also, interestingly, patient's uric acid levels were completely suppressed using the first assay i.e. <0.03 mmol/l (normal 0.1–0.93 mmol/l), but normal (0.23 mmol/l) on repeating with second method.

Factitious results due to assay interference can lead to unnecessary investigations and treatment. Paraproteins can interfere with many laboratory tests including uric acid, glucose, bilirubin, sodium, chloride, phosphate, calcium, high density lipoproteins (HDL), C-reactive protein, thyroxine, urea, creatinine, and albumin. The factitious results are usually due to monoclonal rather than polyclonal immunoglobulins, as in our case. Although pseudohypouricaemia has been reported previously with paraproteins*(1)*, this is the first ever reported case of assay interference manifesting as pseudohypervitaminosis D. We recommend that assay interference should be considered in unexpected abnormal results in the presence of paraproteins, before further investigations and treatment.

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CC09

Deteriorating course of a cystic pituitary lesion during pregnancy

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Rathke's cleft cysts (RCCs) are benign epithelium-lined cystic remnants of the embryonic Rathke's pouch. We report a case of a previously fit and well 30-year-old lady with an incidental finding of a cystic pituitary lesion, discovered when she took part in a clinical trial as a normal volunteer. She had no history to suggest endocrine dysfunction.

Pituitary function tests showed prolactin 302 mU/l (ref <630), LH 2.2 U/l, FSH 4.9 U/l, oestradiol 252 pmol/l, IGF1 186 ug/l (65–350), TSH 1.51 mU/l (0.35–5.00), free T_4 14.4 pmol/l (9.0-21.0), 0900 cortisol 154 nmol/l with 30 minute post-Synacthen cortisol of 493 nmol/l. MRI demonstrated a cystic lesion arising from the pituitary with a height of 14 mm extending into the suprasellar cistern, abutting the inferior optic chiasm. Serial MRI from 2009 to 2011 showed no change. Formal visual field testing was normal. A diagnosis of Rathke's cleft cyst was made.

She fell pregnant in 2013. At 22 weeks gestation, a bitemporal hemianopia was noted. MRI demonstrated enlargement of the lesion to 16.5 mm in height with optic chiasmal impingement. She declined surgical intervention. Visual fields improved spontaneously towards the end of pregnancy. Post-partum MRI confirmed significant regression of the pituitary lesion with resolution of the mass effect on the optic chiasm. It was felt pre-emptive neurosurgical intervention prior to further pregnancy was not indicated. During a subsequent pregnancy in 2016, a temporal visual field defect was noted. The lesion now measured 22mm with optic chiasmal distortion. Transsphenoidal aspiration of the pituitary cyst was undertaken at 25 weeks gestation. Visual field defects resolved. Pituitary function remained intact.

RCCs are often discovered incidentally. Pituitary hormonal axes are altered in pregnancy, often leading to an increase in pituitary size and deterioration of pre-existing pituitary disease. This case highlights the challenges of managing pituitary lesions in pregnancy, and the importance of pre-pregnancy counselling, frequent review and visual field monitoring during pregnancy.

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CC10

Hypoparathyroidism and recurrent hypomagnesaemia since infancy: a rare genetic cause

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We present a diagnostically challenging case of a 22-year old female with short stature and recurrent admissions with severe hypokalaemia, hypocalcaemia and hypomagnesaemia since infancy.

Case

Our patient was born at 38 weeks gestation following a pregnancy complicated by intrauterine growth restriction since 28 weeks. She had low birthweight of 2.4 kg and significantly shorter length and lower head circumference than expected. Mild dysmorphic features of frontal bossing, microphthalmia and mid-facial hypoplasia were evident. Both parents were unrelated, healthy Caucasians of average height.

Her childhood was complicated by growth failure despite normal stimulated GH and IGF-1 levels. Baseline IGF-1 was low at 24 ng/ml. Skeletal surveys showed gracile bones, oligodontia with hypoplastic mandibular condyles and a j-shaped sella. MRI pituitary was normal. She had three trials of GH therapy in childhood which complicated high hypermetropia with macular oedema and visual worsening.

Since infancy, the patient has suffered recurrent and resistant hypocalcaemia, hypomagnesaemia and hypokalaemia requiring frequent hospitalisation. Biochemistry confirms persistent hypoparathyroidism and renal magnesium and potassium loss. Calcium: creatinine ratio, renin and aldosterone were normal. She is treated with alfacalcidol 1 microgram daily and varying doses of calcium carbonate, magnesium and potassium replacement.

An encompassing diagnosis was difficult to achieve, until at the age of 21 years, genomic sequencing confirmed a de-novo heterozygous c.1706G$>$A transition in the FAM111A gene diagnostic of Kenny-Caffey Syndrome 2.

Kenny- Caffey Syndrome 2 (KCS2)

KCS2 is extremely rare with less than 60 cases reported in the English literature. The function of the associated FAM111A gene product isn't fully known but seems to have a fundamental role in bone growth and parathyroid hormone regulation. There is consensus that hypoparathyroidism drives hypocalcaemia but this does not explain the recurrent hypomagnesaemia and hypokalaemia seen in our patient. Further research of the FAM111A gene is needed to better understand this disease presentation.

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